



## The role of gender in social network organization

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# ePosters

## Diagnosis and differential diagnosis

### EP1274

#### Multiple sclerosis, depression and voice: a new tool for diagnosis?

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Prevalence of depression in Multiple Sclerosis (MS) is high (from 27 to 54%) and depression is under-diagnosed. Because of symptoms overlap between depression and MS, diagnostic questionnaires might fail to diagnose depression in MS. Voice study (comprising the uses of voice) is expanding in several fields since the last 10 years: for example, Tsanas *et al.*, (2012) showed that Parkinson disease could be detected precociously from voice thanks to acoustic analyses. To explore if voice analysis could help clinicians to diagnose depression in MS patients, we recorded 2 groups of female speakers: healthy women (28 non-depressed and 25 depressed); and MS patients without dysarthria (32 non-depressed and 30 depressed). Depression was diagnosed according to the Zigmond & Snaith HAD Scale. Our study consists of combining both acoustic measures and judgments made by non-expert listeners, from recorded voices. For each voice recorded, the listeners had to rate pleasantness and depression. We found significant differences in 4 voice parameters between the 2 non-MS groups and the 2 MS groups. For the non-MS groups, the values for the pitch ( $p \leq 0.01$ ), the amplitude ( $p \leq 0.001$ ), the speech rate ( $p \leq 0.05$ ) and the variation of the pitch ( $p \leq 0.01$ ) were higher than in the MS groups. In other words, the voices from the MS groups are lower (in intensity), deeper, slower and less expressive. We found differences between the depressed and the non-depressed women inside each group for 2 parameters: the voices from the depressed women were less expressive ( $p \leq 0.05$ ) and lower ( $p \leq 0.001$ ). The results from the listeners' judgments are similar to those from the voice analyses since non-MS/MS groups and non-depressed/depressed groups could be distinguished (Depression and MS make the voices sound less pleasant). In conclusion, our results highlight that it is possible 1) to detect depression in MS patients using voice analysis; and 2) to distinguish healthy people and MS patients, even if the MS patients with a dysarthria have been excluded.

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### EP1275

#### Comparison of central vein detection in MS at 1.5T, 3T and 7T

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**Introduction:** The central vein sign (CVS) is a new finding in MS studies, which could help improve MS diagnosis. This sign has yet to be studied on 3D isotropic sequences at different magnetic fields, especially on 1.5T for everyday clinical practice. Our purpose was to evaluate the central vein across 1.5T, 3T, and 7T MRI scanners.

**Methods:** Three MS patients from the NINDS (National Institute of Neurological Disorders and Stroke) cohort underwent brain imaging on 3 different MRI scanners (1.5T, 3T, and 7T). Three MS plaques detected on the different scans were selected for each patient. Central vein assessment used a whole-brain high-resolution isotropic T2\*-weighted sequence acquired in under 6 minutes at the three different field strengths. At 1.5T and 3T, this sequence was acquired during, or shortly after, the injection of gadolinium-based contrast agent (GBCA). Assessment of MS plaques and veins were made using the definitions from the 2016 North American Imaging in MS Cooperative consensus statement.

**Results:** Eight out of 9 lesions were central vein-positive on the 3 scanners. Four were located in the deep white matter and 5 were periventricular. Only one lesion had a vein that was visible at 3T and 7T but not at 1.5T.

**Conclusion:** This pilot study indicates that it is possible to detect central veins in MS plaques on 1.5T images with a good reproducibility compared to 3T and 7T images. More MS patients will undergo the same imaging protocol to confirm these initial findings and investigate whether GBCA injection is required at 1.5T and 3T when assessing CVS.

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Pascal Roux: nothing to disclose

Pascal Sati: nothing to disclose

### EP1276

#### Comparison between proton density and T2 weighted sequences for detection of cervical cord lesions in multiple sclerosis

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**Introduction:** Magnetic resonance imaging (MRI) is the gold standard imaging technique for identification of demyelinating lesions such as Multiple Sclerosis (MS). The Consortium of MS Centers Consensus (CMSC) Guidelines has recommended 2D proton density/T2 weighted sequences in standard MS spinal cord imaging protocol. The present study is conducted to compare two major CMSC standard spinal cord sequences, proton density (PD) and T2 weighted images, in the detection of cervical spinal cord lesions of patients with MS.

**Material and methods:** 130 patients with clinically definite MS were imaged during a period from February 2014 to June 2015. 100 of these patients, who had cervical spinal cord lesions were included in this study. An institutional protocol for MS lesion detection consistent with the CMSC clinical guidelines which include sagittal T2-fast spin echo, sagittal T1-fast spin echo, sagittal PD-fast spin echo and axial T2WI through cervical cord from C1/2 to T1 vertebrae, were performed for all included patients. The data were analyzed in order to assess lesion-to-cord contrast ratio (LCR) and lesion-contrast-to-noise ratio (LNR).

**Results:** LCR was significantly higher in T2 weighted images (35.3), in comparison to PD images (24.2). No statistically significant difference was detected between LNR of T2 and PD weighted images ( $P = 0.2$ ). PDWI could not detect the black hole plaques of MS due to more water content of such lesions.

**Conclusion:** Sagittal T2 weighted imaging appears to be superior in comparison to PD sequence for detection of cervical cord MS lesions. Our study questions CMSC guideline in using the PD as a core spinal cord imaging sequence.

**Keywords:** Multiple sclerosis (MS), magnetic resonance imaging (MRI), T2, Proton density (PD), Consortium of MS Centers Consensus (CMSC), Cord lesions

## Disclosure

The authors have no conflict of interest to be declared regarding the manuscript.

## EP1277

### Prognostic factors for multiple sclerosis in patients with isolated spinal syndromes

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**Background:** The early identification of patients with isolated spinal syndromes at high risk of multiple sclerosis (MS) represents the main purpose of the evolving diagnostic criteria and of clinicians in everyday clinical practice. The aim of this study was to investigate the prognostic role of different biomarkers in patients with an isolated spinal syndrome.

**Methods:** We evaluated baseline clinical, MRI, CSF and neurophysiological data of 218 patients (mean age 32.9 years) with a first spinal inflammatory episode. We used discrimination and calibration characteristics and reclassification of risk categories to assess incremental utility of different biomarkers for MS prediction.

**Results:** During follow-up (median 7.3 years), 112 of the 218 participants developed clinically definite MS (CDMS). In Cox

proportional-hazards models adjusted for age at onset and gender, the number of brain T2 lesions ( $>9$  lesions vs  $<2$  lesions, HR 6.5 95% CIs 1.4-15.7), the presence of CSF OCBs (HR 2.3 95% CIs 1.0-4.0) and the multimodal evoked potential score (4<sup>th</sup> quartile vs 1 quartile, HR 2.5 CIs 1.2-4.2) significantly predicted the subsequent development of CDMS. The same biomarkers were significantly associated also with the development of MS according to 2010 diagnostic criteria in the follow-up. The use of multiple biomarkers led to a 27% net-reclassification improvement ( $p < 0.001$ ) over the use of current MRI criteria for MS in the prediction of patients with spinal isolated syndromes who develop multiple sclerosis at 2 years.

**Conclusions:** The simultaneous addition of several biomarkers improves the risk stratification for MS in patients with isolated spinal syndromes beyond that of a model based only on MRI criteria.

## Disclosure

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## EP1278

### Clinical, investigational and outcome profile of acute myelitis in the city of Kolkata, India

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**Background:** Acute Myelitis (AM) could be infectious/ para-infectious or secondary to conditions like multiple sclerosis (MS), neuromyelitis optica (NMO), systemic lupus erythematosus, etc. Besides, AM may be idiopathic where the underlying etiology is undetermined.

**Objective:** In this multi-centric study from India, we aim to determine

(1) the distribution of AM on the basis of etiology and

(2) rate of conversion of AM to MS.

**Method:** In the period 2009-2016, consecutive AM cases were recruited from several centers in the city of Kolkata, India. Compressive, toxic, metabolic, vascular, hereditary and paraneoplastic myelopathies were excluded. Following careful history and examination, all had baseline routine blood, anti-nuclear antibody,

angiotensin-converting enzyme and serum NMO-IgG (cell-based method). Routine CSF analysis and identification of oligoclonal band by iso-electric focusing method were performed. Cerebrospinal MRI with contrast were carried out in all cases. Idiopathic AM cohorts were followed up with cerebrospinal MRI performed annually or earlier if required.

**Results:** Out of the total 64 (men 37, women 27) AM cohorts (age range, 18-54 years; mean  $\pm$  SD,  $37.27 \pm 9.98$  years), there were 12 (18.7%) post-infectious/ infectious and 4 (6.2%) NMO spectrum disorders. In a  $\geq 2$  year follow up of 24 idiopathic AM cohorts, 8 (33.3%) converted to MS. Six individuals had recurrent AM but they had no evidence of MS or NMO. All who converted to MS had 1 or more cerebral lesions at baseline, whereas none of those who failed to convert had any cerebral lesion.

**Conclusion:** The conversion rate from idiopathic ON to MS in our study is similar to that in the Western countries. On the other hand, NMO spectrum disorder is more prevalent in our country.

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2. Ghosh E: nothing to disclose
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### EP1279

#### Evaluation of the predictive value of three serum and CSF biomarkers for the development of clinically definite multiple sclerosis (CDMS) following an initial clinically isolated demyelinating event (CIS)

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**Objective:** To evaluate the possible correlation of the presence in the serum and/or CSF of Tau protein, CXCL13 and Neurofilaments, with the risk of developing Clinically Definite MS, following an initial clinically isolated syndrome CIS.

**Design and methods:** 29 patients with CIS from our MS Centre at Hadassah were included in a prospective study in addition to 23 controls and followed up for 1-5 years. The primary end point of the study was the conversion from CIS to CDMS. We compared the percentage of patients who were positive for 1 or more of the suggested biomarkers in their sera/CSF who developed CDMS after 1-5 years of follow up, with the percentage of those who were negative for the same biomarkers. A secondary end point was to establish a quantitative correlation between the levels of the biomarkers in the serum and/or CSF and the probability of conversion to CDMS. ELISA was used for measurement of the serum and CSF levels of the fore mentioned biomarkers.

**Results:** During the follow up period, 20 patients were finally diagnosed with CDMS and 9 patients remained as CIS with

similar gender distribution between the two groups. A significant difference between the values of 2 of the tested biomarkers (CXCL13 and neurofilaments) in the sera of patients who converted to CDMS as compared to patients who remained CIS throughout the study period. 75% of patients and 70% of patients who were diagnosed as CDMS tested positive for CXCL13 or NFL in their serum vs only 1 out of 9 (for either CXCL13 or NFL) who remained as CIS (P value 0.0009 with a median value of 9 pg/ml for CIS patients and a median value of 48.5 pg/ml for CDMS patients, risk ratio 6.75, odds ratio 24 from CXCL13; median level of NFL 622 pg/ml for CIS vs 1119 pg/ml for CDMS patients). Double positivity was found to have a strong negative predictive value as zero percent of the CIS patients were double positive, and 10 out of 20 CDMS patients (50%) were found to be positive for both CXCL13 and NFL (95% confidence interval, risk ratio of 2 and odds ratio approaching infinity value). The values in the CSF were insignificant which could be attributed to the long period of preservation of the CSF or could signify the need of more sensitive methods for their measurement. Tau levels were not significant neither in the CSF nor in the sera of the tested population.

**Conclusions:** CXCL13 and neurofilaments in the serum of patients with CIS, may represent significant predictive biomarkers for conversion to CDMS

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### EP1280

#### Anti-MOG-IgG associated syndromes: report of 22 cases

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**Background:** Serum anti-myelin oligodendrocyte glycoprotein antibodies (MOG-IgG) have been described in different CNS inflammatory disorders. We report longitudinal clinical, MRI and



CSF data of a series of patients seronegative for anti-aquaporin-4 antibody (AQP4-IgG) and positive for MOG-IgG.

**Methods:** A commercial cell-based assay was used to analyze AQP4-IgG, while a live-cells (HEK293A) immunofluorescence assay was used for the detection of MOG-IgG with a positive titer cut-off set at 1:160. Consecutive serum samples referred to Verona University Neuropathology Laboratory for AQP4-IgG/MOG-IgG testing were analyzed between March 2014 and April 2017.

**Results:** Among 444 tested patients, 22 MOG-IgG positive cases (13 females) were identified. In the 4 weeks before the onset, 10 patients had fever, upper respiratory tract and/or gastrointestinal infection and one received anti-influenza vaccination. Three cases had serological evidence of a recent infection with HSV1, *Borrelia burgdorferi*, and Cytomegalovirus. Clinical presentation included optic neuritis in 10 cases, myelitis in 10, both in one and confusion and lethargy in one subject. In addition, cerebellar and/or brainstem signs were present in two patients. Eleven patients experienced relapses. Spinal cord MRI showed short lesions in 11 patients, and longitudinally extensive lesions in 3 subjects. Seven patients had CSF pleocytosis and/or increased protein level, while 4 had CSF oligoclonal bands. Recovery was partial in 17 cases, complete in 3, and absent in 2. Of 6 patients retested for MOG-IgG after 3-168 months from the index event in absence of relapses, 4 resulted negative while 2 were positive, at a lower titer compared to initial test.

**Conclusion:** Serum MOG-IgG are associated with neurological syndromes usually characterized by involvement of the spinal cord and optic nerve. In rare cases a syndrome resembling viral or autoimmune encephalitis can also be the presenting feature. MOG-IgG are preceded or accompanied by an acute infection and followed by relapses in half of cases. Most patients have neurological sequelae. It is essential to test MOG-IgG in the acute phase since antibody titer tends to decrease in non-relapsing patients.

## Disclosure

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## EP1281

### Cerebrospinal fluid CD4+/CD8+ ratio in diagnosing neurosarcoidosis

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**Background:** Neurosarcoidosis affects between 5-10 % of all sarcoidosis patients and is a major differential diagnosis to multiple sclerosis. Diagnosing neurosarcoidosis becomes particularly difficult when it appears primarily in the nervous system and is a challenge to the neurologist. It has previously been suggested that an elevated cerebrospinal (CSF) CD4+/CD8+ ratio >5 can be an aid in diagnosing neurosarcoidosis.

**Method:** In this study we studied the cases of 66 patients who were subject to the analysis of CSF CD4+/CD8+ ratio by flow cytometry where neurosarcoidosis was a differential diagnosis. The final diagnoses from patient charts were sub-grouped into sarcoidosis, other neuroinflammation and non-inflammation.

**Results:** We found 11 cases of neurosarcoidosis who, as a group, had a higher mean CSF CD4+/CD8+ ratio than the other two groups, with a significant difference only against the non-inflammatory group.

The mean CSF CD4+/CD8+ ratio was 4.39, hence not reaching the suggested level of >5 for diagnosing neurosarcoidosis. We added the elevated CSF CD4+/CD8+ value >5 together with an elevated CSF lymphocyte count (2xULN) and found a positive predictive value of 60 % and a high negative predictive value of 92 %.

**Interpretation:** CSF CD4+/CD8+ ratio >5 measured by flow-cytometry in combination with elevated lymphocyte-count is a method that can be utilized in diagnostic workup in neurosarcoidosis.

## Disclosure

CM has received lecture honoraria and served on AdBoards for Biogen, Merck, Novartis and Sanofi-Aventis.

SN and BA has no conflict of interest and nothing to disclose.

## EP1282

### Changes in the profile of patients with multiple sclerosis over the last 30 years due to evolution of diagnostic criteria

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**Aim:** The main purpose of this study was to investigate demographic and clinical characteristics of patients with multiple sclerosis (MS) diagnosed according to different criteria between 1986 and 2015.

**Material and methods:** We analysed medical records of patients with MS diagnosed between 1986 and 2015. The patients were divided into 4 separate subgroups according to following criteria: A) Poser, n=145, B) McDonald 2000, n=66, C) McDonald 2005, n=62, and D) McDonald 2010, n=60. We aimed to investigate: 1) demographic characteristics, including sex and age, 2) the time between first symptoms suggestive of MS and confirmed diagnosis of MS, 3) severity of impairment at diagnosis assessed with the EDSS and symptoms that prompted workup for MS.

**Results:** We included 333 patients with definite MS. The female-to-male ratio for the whole group was 2.3:1, whereas in subgroups

it differed significantly (A - 1.9; B - 1.6; C - 4.6; D - 3.6, A vs D,  $p=0.001$ ).

The mean age at diagnosis decreased gradually in subsequent groups (A -  $39.6 \pm 13.3$ ; B -  $37.7 \pm 12.8$ ; C -  $35.4 \pm 13.0$ ; D -  $29.9 \pm 9.3$  years,  $p < 0.001$ ). Moreover, the time from the first symptom suggestive of MS to confirmed diagnosis shortened significantly (A -  $88.9 \pm 80.2$ ; B -  $39.1 \pm 68.4$ ; C -  $36.2 \pm 58.4$ ; D -  $33.5 \pm 68.2$  months,  $p < 0.0001$ ). The disability level measured at diagnosis on the EDSS decreased in consecutive subgroups (A -  $4.4 \pm 2.2$ ; B -  $3.1 \pm 1.7$ ; C -  $2.7 \pm 1.3$ ; D -  $2.8 \pm 1.4$ ). Pyramidal symptoms remained the most common manifestation of the disease at diagnosis regardless of the diagnostic criteria (A - 50.34%, B - 54.55%, C - 32.26%, D - 31.67). However, an increasing trend for visual dysfunction was observed (A - 15.9%, B - 14%, C - 19%, D - 23.3%; A vs. D,  $p < 0.0001$ ).

**Conclusions:** Our study indicates a significant change in demographic and clinical characteristics of patients with MS diagnosed according to the relevant criteria. Over the analysed period, the diagnosis was made at a younger age and more often in women, the time gap between first symptoms suggestive of MS and confirmed diagnosis shortened, and disability at diagnosis decreased.

## Disclosure

Nothing to disclose

## EP1283

### The MRZ reaction in rheumatological disorders with CNS involvement and primary CNS lymphoma

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**Introduction:** The MRZ reaction (MRZR), composed of the three respective antibody indices (AI) against measles, rubella and varicella zoster virus, has been found positive almost exclusively in patients with multiple sclerosis (MS)<sup>1-2</sup>. Rheumatological disorders with involvement of the central nervous system (RDwCNS) and primary CNS lymphoma (PCNSL) can display similar symptoms, MRI findings and cerebrospinal fluid (CSF) routine results compared to MS and thus may be difficult to distinguish from MS but require a different therapy.

**Methods:** MRZR-2 (defined as positive by at least two  $AI \geq 1.5$ ) was assessed in patients with RDwCNS ( $n = 23$ ), PCNSL ( $n = 37$ ), MS ( $n = 203$ ) and patients with a schizophreniform or bipolar disorder ( $n = 76$ ). MRZR-2 results were compared using the Fisher's exact test (two-tailed) with  $p < 0.05$  for statistical significance.

**Results:** Demographic data of all study cohorts are shown in Table 1. MRZR-2 results are presented in Figure 1. A positive MRZR-2 was statistically significantly more frequent in MS patients (48.8%) compared to RDwCNS (8.7%), PCNSL (8.1%) and psychiatric patients (2.6%;  $p < 0.001$  for all comparisons with the MS group).

**Discussion:** These MRZR-2 results confirm the comparable high specificity for MS also in the context of RDwCNS and PCNSL and thus indicate its potential as a diagnostic tool to differentiate these diagnoses from MS. Nevertheless, a brain biopsy remains

the diagnostic gold standard for PCNSL. In respect of rheumatological disorders detection of extractable nuclear antigens (ENA) is helpful in case of present antinuclear antibodies (ANA), because MS patients show slightly elevated unspecific ANA titers in around 30% as well<sup>3</sup>.

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## Disclosure

### Conflicts of interest

TH, RD, and DE: nothing to disclose.

SR and OS have received consulting and lecture fees and grant and research support from Baxter, Bayer Vital GmbH, Biogen Idec, Genzyme, Merck Serono, Novartis, RG, Sanofi-Aventis and Teva. NV has served on advisory boards of, has participated in lectures for, and/or received research or travel grants from AbbVie, GSK, Janssen-Cilag, Lilly, Medac, Novartis, Pfizer, and Roche.

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## EP1284

### Role of visual evoked potentials in spatial dissemination for multiple sclerosis diagnosis

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**Background:** Multiple Sclerosis (MS) diagnosis is based on clinical and para-clinical tools to demonstrate dissemination in space (DIS) and time. Although Visual Evoked Potentials (VEPs) are commonly used in MS diagnosing, 2010 diagnostic criteria (DC, Polman Ch et al.2011)) did not include the optic nerve (ON) within typical sites considered to meet DIS. In 2016 MAGNIMS (Filippi et al, 2016) group proposed, inclusion of optic nerve (ON) lesions and alteration of VEP parameters to demonstrate DIS. A further proposal from the MAGNIMS group is to use a more restrictive criterion to locate the periventricular involvement (at least 3 lesions).

The aim of our study is to evaluate whether the inclusion of VEPs among the typical sites of demyelinating disease allows to anticipate the diagnosis of MS.

**Material and methods:** We retrospectively evaluated patients hospitalized between 2010 and 2015. All patients included were subsequently diagnosed with MS. For all patients included were detected major clinical and demographic variables, MRI of the brain and spinal cord, VEPs were performed at the time of hospitalization for MS diagnosis.

We evaluated 4 DIS definitions:

- **4 areas DIS** (according to 2010 DC: involvement of at least 2 of the following 4 CNS areas: iuxtacortical, periventricular, infratentorial and spinal cord demonstrated on MRI);

- **4 areas DIS plus VEPs** (involvement of at least 2 areas of the following 5 CNS areas: iuxtacortical, periventricular, infratentorial and spinal cord demonstrated on MRI or ON demonstrated by VEPs);

- **3 Areas DIS** (involvement of at least 2 of the following 3 MRI areas: supratentorial, infratentorial and spinal cord);

- **3 Areas DIS plus VEPs** (involvement of at least 2 of the following 4 CNS areas: supratentorial, infratentorial and spinal cord demonstrated on MRI or ON demonstrated by VEPs).

**Results:** We included 200 MS patients. At the time of hospitalization, space dissemination was demonstrated in 154 /200 patients (77%) using 4 areas DIS and in 174 / 200 patients (87%) using 4 areas DIS plus VEPs, in 121 / 200 patients (60.5%) using 3 areas DIS and in 153/200 (76.5%) using 3 areas DIS plus VEPs.

**Discussion and conclusion:** Integrating VEPs into DIS allows to anticipate diagnosis in 10% of patients by supplementing DC 2010 and 16.5% using a more restrictive MRI criterion. Our data support the importance of assessing ON involvement through VEPs to achieve DIS according with the MAGNIMS group proposes.

## Disclosure

Dr. Fenu, Frau, Coghe, Lorefice received consulting fees from Biogen Idec, Merck Serono, Teva, Genzyme, Roche, Novartis.

Prof. Cocco and prof. Marrosu received honoraria for lecturing, travel expenses for attending meetings and financial support for research from Bayer Schering, Biogen Idec, Sanofi-Aventis, Novartis and Merck Serono,

Dr Maggiore: nothing to disclose

Dr. Arru: nothing to disclose

## EP1285

### Integrin and IL-16/IL-23 biomarker clusters differentiate AQP4-IgG+ NMO spectrum disorders, relapsing-remitting MS and healthy controls

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**Background:** Neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS) are relapsing inflammatory diseases of the CNS. NMOSD is caused by antibodies against aquaporin 4 (AQP4) in the majority of cases.

**Objectives:** To examine if soluble biomarkers of endothelial stress, cytokines, and chemokines can differentiate AQP4+NMOSD

from relapsing-remitting multiple sclerosis (RRMS) and correlate with the levels of anti-AQP4.

**Methods:** We examined serum from 46 patients with anti-AQP4+NMOSD, 30 patients with RRMS and 22 healthy subjects (HS). IgG and IgM anti-AQP4 antibodies were determined by cell-based flow cytometry assays with human glioblastoma cell line stably transduced using a lentiviral vector to overexpress human AQP4-M23. Twenty-six biomarkers were measured by the Mesoscale Discovery technique.

**Results:** Hierarchical clustering was able to differentiate AQP4+NMOSD and RRMS. Correlation among biomarkers defined major clusters of endothelial stress (VCAM, ICAM, SAA), IL-12p40/IL-23 and IL-16, and an inflammatory cluster including IL-8, IL-1b, TNF-a, IL-6, IL-12p70. Seventeen biomarkers were differently expressed in AQP4+NMOSD compared to RRMS; among them, IL-6, IL-8, IL-16, and IL-12p40/IL-23 were significantly increased in AQP4+NMOSD and MS compared to HS. Concentration of biomarkers did not correlate levels of AQP4 IgG in the sera. Decision tree defined the endothelial cluster important in AQP4+NMOSD and RRMS differentiation, and the IL-12p40/IL-23/IL-16 cluster further differentiating RRMS from HS.

**Conclusion:** Elevated levels of biomarkers and biomarker cluster reflecting endothelial stress (VCAM, ICAM, IL-6, IL-8) may differentiate AQP4+NMOSD from RRMS, while Th17 expansion may be important in both diseases reflected by elevated levels of IL-23 compared to HS.

## Disclosure

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TS:has received grant support and consultation fees from Biogen Idec, Novartis, Teva and Genzyme as well as the Danish Multiple Sclerosis Society and the region of Southern Denmark Research Fund.

ZI: has received grant support and consultation fees from Biogen Idec, Novartis, Teva and Genzyme as well as the Danish Multiple Sclerosis Society and the region of Southern Denmark Research Fund.

TP: has received grant support and consultation fees from Biogen Idec, Novartis, Teva and Genzyme as well as the Danish Multiple Sclerosis Society.

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SK: nothing to declare

TF: nothing to declare

TC: nothing to declare

GL: nothing to declare

MS: nothing to declare

TM: nothing to declare

JB: nothing to declare

## EP1286

### Frequency of anti-AQP4 and anti-MOG antibody positivity in patients with demyelinating diseases in Rio de Janeiro / Brazil



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The oligodendrocyte myelin glycoprotein (MOG) is a potential target of cellular and humoral response in the inflammatory process of demyelinating diseases of the Central Nervous System (DDs). Anti-Aquaporin 4 receptor antibodies (AQP4) are sensitive serologic markers of autoimmunity in Neuromyelitis Optica (NMO) and NMO spectrum disorders. Both can be used for diagnosis and differential diagnosis of these syndromes and can be performed by two laboratory methods, indirect immunofluorescence (AQP4) and live cell based assays for AQP4 and MOG. The frequency of antibody positivity against AQP4 and MOG- using the live cell based assays for AQP4-Abs and antibodies against MOG was investigated in patients with DDs treated in 2016 at a reference center in Rio de Janeiro/Brazil. A total of 67 patients were evaluated: Multiple Sclerosis (MS): 7 patients; Acute disseminated encephalomyelitis (ADEM): 3 patients; Optic-spinal Multiple sclerosis (OS-MS): 9 patients; NMO: 26 patients; Recurrent bilateral optic neuritis (RON): 16 patients and Transverse Myelitis (TM): 6 patients. 21 patients were seropositive for AQP4 and 3 for MOG. According to the diagnosis distribution, positive for AQP4: NMO: 50% (13/26); RON: 25% (4/16); TM: 33% (2/6); other cases were seronegative. Positive for MOG was observed in 2 patients with RON and 1 patient with TM after infection by Zika virus. Regarding NMO patients, the frequency of anti-AQP4 positivity was 50%, comparable to the results obtained by indirect immunofluorescence method already described in the literature, as well as in cases of RON (25% positivity) and TM (33%). Regarding anti-MOG screening, it was not observed in most patients, except in 2 NOR patients (12.5%) and one case of post-infectious myelitis by the Zika virus, the first described in the literature so far. There was no simultaneous positivity between AQP4 and anti-MOG in this series.

## Disclosure

Vanderson Neri: nothing to disclose  
Alexandre Lopes: nothing to disclose  
Elizabeth Batista: nothing to disclose  
Solange Camargo: nothing to disclose  
Ana Carolina Araujo: nothing to disclose  
Marcos Alvarenga: nothing to disclose  
Cleoneice Bento: nothing to disclose  
Priscila Barros: nothing to disclose  
Claudia Vasconcelos: nothing to disclose  
Regina Alvarenga: nothing to disclose

## EP1287

### Serum aquaporin-4-IgG and MOG-IgG in patients with an initial demyelinating event: protocol and preliminary results of an Italian prospective multicentre study

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**Introduction:** Serum anti-Myelin Oligodendrocyte Glycoprotein antibodies (MOG-IgG) have been detected in patients with various demyelinating disorders. However, the lack of prospective studies leaves uncertainty on the clinical significance of MOG-IgG detection. This study is aimed at clarifying the diagnostic and prognostic value of MOG-IgG testing in patients with demyelinating events and presentation features atypical for MS.

**Methods:** 16 Italian centres will participate in the study. Eligible patients are aged 18-80 years, with a first demyelinating event occurred within 12 months from screening and not fulfilling 2010 McDonald criteria for MS. Each patient will be followed prospectively for 2 years, with baseline evaluation including clinical assessment, brain and spine MRI, lumbar puncture, and evoked potentials. Serum aquaporin4 (AQP4)-IgG and MOG-IgG testing will be performed at Verona Neuropathology Laboratory using a commercial fixed cell-based assay for AQP4-IgG and an in-house live cell-based immunofluorescence assay for MOG-Ig (positive cut-off titre  $\geq 1:160$ ). Clinical assessment will be repeated every 6 months, while MRI and evoked potentials annually. AQP4-IgG and MOG-IgG will be retested in case of relapse and every 6 months in seropositive patients.

**Results:** By May 2017, 15 patients (11 females) have been enrolled in 3 centres. Median onset age was 43 (25-59) years and follow-up duration was 6 (0-12) months. Clinical presentation was optic neuritis in 7, acute myelitis in 6, and other in 2 cases. Three patients were MOG-IgG positive at baseline, while one was AQP4-IgG positive. Compared to MOG-IgG negative, MOG-IgG positive cases had more frequently severe presentation (median EDSS score at nadir 2.0 vs. 3.5), longitudinally extensive spinal lesions on MRI (20% vs. 100%), CSF pleocytosis  $>50/\mu\text{l}$  (0 vs. 67%), and absence of CSF-restricted oligoclonal bands (30% vs. 67%). MOG-IgG assay was repeated at 6 months in 2 initially positive patients and it resulted negative in both cases.

**Conclusions:** In this prospective multicentre study we recruited adult patients with non-MS demyelinating events and we performed a comprehensive evaluation including serum AQP4-IgG and MOG-IgG assessment. Our results suggest that MOG-IgG positivity seems to be around 20% in this population and is associated with distinct MRI and CSF features. MOG-IgG needs to be tested as early as possible after clinical onset as seropositive cases may become negative in few months.

## Disclosure

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#### EP1288

##### **detection of anti mog antibodies in demyelinating disorders of the central nervous system (CNS)**

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MOG is a CNS-specific antigen expressed on the surface of myelin sheaths. Anti MOG antibodies (Abs) have been recently described as diagnostic marker of acquired demyelinating CNS diseases different from Multiple Sclerosis (MS), as seronegative Aquaporin-4 Neuromyelitis Optica spectrum disorders, pediatric ADEM or very early onset pediatric MS. To date there is not a standardized protocol to detect anti-MOG Abs although the most specific methods are cell based assays (CBA). Here we present our work to set up the FACS procedure for routine detection.

Glial LN18 cell line untransfected or stably transfected with full-length MOG were provided by Hemmer lab (Monaco). They were incubated with patients' sera, marked with anti-human IgG secondary antibody and analyzed by FACS. In each assay we tested 4 internal controls: 1 healthy commercial serum (NC), 1 purified anti-MOG Ab, 1 human IgG anti-MOG+ patient serum and 1 human IgG1 anti-MOG+ patient serum. We expressed the Ab titers as the difference in median fluorescence intensity ( $\Delta$ MFI) between the MOG-transfected and untransfected LN18. The  $\Delta$ MFI threshold was 23, i.e. the average  $\Delta$ MFI plus 6 SD of healthy control (HC). Values higher than 23 were tested again to evaluate the IgG subclasses.

Medium values of positive controls were 1982 for purified anti-MOG Ab and 357 for IgG anti-MOG+ human sample. The low and high CBA detection limits were assessed using serial dilution of both positive controls ( $R^2 = 0.99$ ). All 61 HC and 13 MS tested sera were negative for anti-MOG (mean  $\Delta$ MFI 2.5, SD 3 and mean 1.5, SD 2, respectively). No differences were found between HC and MS, while the difference between HC and both positive controls was significant ( $p < 0.0001$ ). From June 2015 to April 2017 we performed 570 anti-MOG Ab detections on 488 patients from different Italian neurology department. Cross reactivity to AQP4 and MOG was never detected at the same time. We identified 21 IgG anti-MOG+ patients (4.3%), mostly IgG1, except for one IgG3. We identified also 4 BORDERLINE PATIENTS with Ab titre around the threshold. In this case we suggested a retest after 3 months. In fact, 1 of these patients became IgG1 anti-MOG+ 3 months later.

Our CBA test is reliable and reproducible and do not provide false positive results. We are the only one Italian laboratory offering a CBA test for diagnostic routine. The anti MOG detection represents a new diagnostic tool to discriminate from different inflammatory CNS diseases.

#### **Disclosure**

Marco Capobianco received speaking honoraria from Almirall, Biogen, Merck-Serono, Novartis, Sanofi-Genzyme, TEVA and served in advisory board for Biogen, Novartis, Merck-Serono, Bayer, Roche

Antonio Bertolotto received honoraria for serving in the scientific advisory boards of Biogen, Merck, Mylan, Sanofi-Genzyme, and received speaker honoraria from Biogen, Genzyme, Novartis, TEVA; his institution has received grant support from Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, TEVA, from the Italian Multiple Sclerosis Society, Fondazione Associazione Ricerca Biomedica ONLUS and San Luigi ONLUS.

Arianna Sala received honoraria from Biogen.

Michela Spadaro received honoraria from Biogen.

#### EP1289

##### **Which treatment strategies for highly refractory forms of Neuro-Behçet disease?**

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**Introduction:** Over the past years, the use of anti-tumor necrosis factor-  $\alpha$  (TNF-  $\alpha$ ) agents and IL-6 blockade by tocilizumab for the management of Neuro-Behçet disease (NBD) has increased progressively, but still remains off-label. However, some patients remain refractory and warrant a different approach to treatment.

**Objective:** To describe a case of NBD refractory to traditional immunosuppressive agents with secondary failure of anti-TNF- $\alpha$  and anti-IL-6 therapies.

**Methods and results:** We present the case of a 32-year-old male patient with a history of recurrent oral ulcerations, bilateral anterior uveitis, papulo-pustular skin lesions, erythema nodosum on both legs. He was diagnosed with NBD after presenting T2/FLAIR hyperintense white matter lesions in the midbrain and hypothalamus showing Gadolinium-enhancement, responsible for cerebellar syndrome, diplopia and hypersomnia. The International Criteria for BD were fulfilled and azathioprine (AZT) 150mg/day combined with oral steroids started. Following 2 relapses at 12 and 18 months respectively after starting AZT, monthly pulses of intravenous cyclophosphamide (1000 mg) were started but the patient relapsed again 8 months later. Given the aggressive disease course, anti-TNF $\alpha$  therapy with infliximab (INFX) was started (5 mg/kg every 8 weeks), in combination with 100 mg of AZT and oral steroids. The patient remained relapse-free both clinically and radiologically until he presented a severe spinal cord relapse with paraplegia and paresis of upper limbs 26 months after starting INFX. Tocilizumab infusions were started (8 mg/kg/month) but did not lead to remission as 2 subsequent relapses were observed within 3 months. The patient was started on another anti-TNF- $\alpha$  agent (golimumab). He remains free of disease activity 4 months later.

**Conclusion:** NBD is a devastating CNS inflammatory disease for which there is an unmet need for effective therapies in patients failing several lines of immunosuppressive treatment to avoid unfavourable outcome. Randomized controlled trials or pragmatic trials are needed to determine the best treatment algorithm.

#### **Disclosure**

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#### EP1290

##### Neuromyelitis optica spectrum disorders with myelin oligodendrocyte glycoprotein or aquaporin-4 antibodies: clinical and paraclinical characteristics in Algerian patients

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Neuromyelitis optica (NMO) is a severe autoimmune inflammatory disorder of the central nervous system. NMO and its abortive forms are referred to as NMO spectrum disorders (NMOSD). NMOSD are mostly associated with antibodies to aquaporin-4 (AQP4-IgG). However, recent studies have demonstrated antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) in a subset of patients. The data on NMOSD in North Africa are sparse.

**Objective:** To describe the frequency of MOG-IgG and AQP4-IgG among patients with optic neuritis (ON) and/or myelitis in Algeria as well as the clinical and paraclinical features associated with these antibodies.

**Methods:** Retrospective testing of 42 patients treated at the teaching hospital of Tizi Ouzou for MOG-IgG and AQP4-IgG, and retrospective evaluation of the patients' medical records.

**Results:** Six of 42 (14.3%) patients were positive for AQP4-IgG and 3/42 (7.1%) were positive for MOG-IgG. No patient was positive for both AQP4-IgG and MOG-IgG. All antibody-positive patients were women. MOG-IgG was associated with severe episodes of ON in all MOG-IgG-positive patients. Steroid treatment was followed by complete remission in two patients. AQP4-IgG was associated with ON and/or longitudinally extensive transverse myelitis (LETM), often with severe onset. While all six of the AQP4-IgG-positive patients met the 2015 IPND criteria for NMOSD, only one of the three MOG-IgG-positive patients did so. Interestingly, clinically silent extensive spinal cord or brain lesions were present in two of the three MOG-IgG-positive patients, and altered visual evoked potentials without clinical evidence of ON were found in three of the six AQP4-IgG-positive patients.

**Conclusion:** MOG-IgG and AQP4-IgG are found in a substantial subset of Algerian patients with ON and/or myelitis, are present predominantly in women, and may be associated with differences in clinical presentation and, possibly, outcome. Only a subset of MOG-IgG positive patients meets the current diagnostic criteria for NMOSD.

#### Disclosure

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assays (AQP4 and anti-neuronal antibodies) and for MOG and AQP4 antibody validation experiments organized by Euroimmun (Germany).

#### EP1291

##### Not all optic neuritis are multiple sclerosis: drusen and paraneoplastic autoimmune disease as cause of optic neuropathy in young people

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**Background and objective:** The most frequent cause of visual loss in young adults is optic neuritis, whose pathogenesis is usually inflammatory and demyelinating. Up to 75% of the cases will meet multiple sclerosis (MS) criteria in 15 years. But there are other pathologies that can mimic optic neuritis and should be included in the differential diagnosis. We report two cases of optic neuritis, uncommon in the literature, and to be taken into account in the differential diagnosis of MS.

**Method:** Case report of a 14-year-old man with a optic neuritis 2<sup>a</sup> to drusen and a case report of a 41-year-old man with a optic neuropathy caused by antibody anti recoverina.

**Results:** We report a case of a 14-year-old man who goes to the emergency room for a blurred vision of the left eye, eminently in the lower field, without added pain. He was seen by the ophthalmology service, that warn pseudo edema papila, advising assessment by the neurology service and review by them the next day. That day, they noticed splinter hemorrhages around the papilla motive for which they entered the neurology service. Brain CT, OCT and ultrasound were obtained, which evidenced papilla drusen. Diagnosis of non-arteritic ischemic optic neuritis secondary to drusen was issued. A 47-year-old man who visited the neurology service due to episodes of vision of spots in the right eye and double vision, lasting minutes, that were repeated 2 to 3 times a month. As personal background he referred Hodgkin's disease, treated with bone marrow transplantation 10 years earlier. No abnormalities in the review by the ophthalmology service. Brain MRI with peri-ventricular demyelinating lesions, negative oligoclonal bands, pathological evoked potentials, and anti-recoverine positive body. He was diagnosed of paraneoplastic syndrome.

**Conclusions:** Although multiple sclerosis is a relatively frequent disease in young people with optic neuritis, other diseases have to be considered in the differential diagnosis of these diseases. It is necessary to recognize those atypical forms of optic neuritis in which the aetiological study must be extended. Important advances have been made in the knowledge of some of them thanks to the determination of specific markers.

#### Disclosure

nothing to disclose

#### EP1292

##### Brainstem syndrome and longitudinally extensive transverse myelitis (LETM) as first manifestation of Adult T-Cell Leukemia/Lymphoma (ATLL)

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**Introduction:** Multiple sclerosis and neuromyelitis optica are the most common inflammatory disorders of the central nervous system (CNS) and commonly initially present as brainstem syndromes or myelites. They can be mimicked by other inflammatory systemic diseases. We report a fatal case of Chronic Adult T-Cell Leukemia/Lymphoma (ATLL) which initially manifested as a brainstem syndrome associated to a longitudinally extensive transverse myelitis (LETM).

**Case presentation:** A 38 year old previously healthy female was admitted to our service with a one and a half month history of corticosteroid unresponsive tetraparesis with a sensory level and brainstem symptoms. She had a family history of HTLV-I-associated myelopathy/tropical spastic paraparesis.

Blood workup revealed significant leukocytosis, positive human T-lymphotropic virus (HTLV) serum screening test and normal cerebrospinal fluid analysis. Magnetic resonance imaging displayed multiple tumefactive lesions with contrast enhancement primarily in the pons with extension to the remaining of the brainstem, cervical and thoracic spine. High dose intravenous methylprednisolone was initiated with no clinical response. In spite of treatment the patient developed a locked in syndrome with acute ventilatory failure within days of admission. Plasmapheresis was initiated. Subsequently, a peripheral blood smear found the presence of "flower cells" with a positive CD25 marker - a diagnosis of Chronic Adult T-Cell Leukemia/Lymphoma (ATLL) was performed and specific treatment (interferon alpha-2b and zidovudine) was offered. Despite our efforts the patient passed away due to severe dysautonomia. *Post mortem* analysis revealed nonspecific perivascular and parenchymal lymphocytic infiltrates with no positivity to anti-aquaporin-4 or lymphoma markers.

**Discussion:** Worldwide approximately 10-20 million people are infected with HTLV. The risk of development of ATLL amongst infected patients is 2-5%, few of which will ever present neurologic symptoms. There are few reports of ATLL with CNS involvement as an initial manifestation- it is even rarer in the chronic subtype. To the best of our knowledge this is the first case of chronic ATLL opening with a rapidly progressive corticosteroid unresponsive brainstem syndrome.

**Conclusion:** Inflammatory disorders of the CNS comprise a range of differential diagnosis. A high level of suspicion is needed in order to perform timely differential diagnosis and offer treatment.

## Disclosure

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## EP1293

### In-vivo axon diameter dynamics in clinically isolated syndrome: a powerful biomarker in early diagnosis of MS

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**Introduction:** Patients with Clinically Isolated Syndrome (CIS) are at extremely high risk to develop multiple sclerosis (MS). However, a prediction tool of CIS patients that will early convert to MS, is missing. AxCaliber is an innovative MRI based technology that enables in-vivo measurements of axon diameter dynamics in healthy population and MS patients.

**Objective:** Evaluate whether measurements of axon diameter distribution (ADD) dynamics will predict CIS patients that will convert to MS within 1 year from diagnosis.

**Methods:** 12 CIS patients, 9 females, age 34.0±9.6; disease duration 0.22±0.1 years; EDSS 1.3±0.7; without any lesions in the mid-sagittal plane of the corpus callosum (CC) performed brain MRI examination 3T (GE) using AxCaliber-1D protocol. Images were used to calculate ADD following the representation of each CC voxel by gamma-distribution expected value. CIS data was then inserted to our MS classifier to early detect MS from CIS cohort. CIS patients were followed up for 12 months.

**Results:** CIS patients showed significant lower ADD values than healthy controls (2.5mm±0.27 and 3.5mm, respectively, P<0.001) and similar diameter sizes compared to MS patients (2.5mm±0.18, P>0.05). ADD was the only significant parameter among other MRI data (mean diffusivity (MD), fraction anisotropy (FA) and CC volume, all P>0.05) that differentiated between CIS and MS. Our classifier, which uses ADD, MD values and age, classified 11 CIS as MS and one as non-MS. After 12 months, all 11 CIS who were classified as MS were definitively diagnosed as MS (all had dissemination in space).

**Conclusions:** The ability to early detect reduction in axon diameter in the CIS stage, will allow early treatment of MS and provide better disease outcomes.

## Disclosure

Assaf Horowitz - Nothing to disclose  
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## EP1294

### Misdiagnosis of multiple sclerosis and common alternate diagnoses

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**Background:** Diagnosing multiple sclerosis involves evaluation of the patient history, examination, imaging, and ancillary testing. No one test can rule in nor rule out MS, and many diseases can mimic the often vague symptoms of MS or cause white matter lesions in the central nervous system. While specific diagnostic criteria exist with revisions under review, there is still room for error in this process. A survey of MS specialists found that 94% had evaluated at least one patient in the last year who had an incorrect diagnosis of MS. Studies of groups of misdiagnosed patients found migraine and psychiatric disease to be the most common correct diagnoses. We evaluated the referrals to our subspecialty multiple sclerosis clinic in an effort to understand the types of and reasons for these errors.



**Objectives:** To identify the incidence of misdiagnosis of MS and any patterns or common mistakes that lead to these errors.

**Methods:** All new consults seen in an MS clinic from July 2016 - May 2017 were evaluated and categorized by initial diagnosis on referral, category of disease, and correct diagnosis after appropriate workup was completed. The 2010 McDonald criteria were used and, when necessary, lumbar puncture, serum, and evoked potentials testing. 142 new patient consults were completed in this time and included in this study. This study was reviewed and approved by the institutional review board of the University of California, Los Angeles.

**Results:** 32% of new patients did not meet diagnostic criteria for MS or were felt to have a much more likely alternate diagnosis. 9% of these non-MS patients were on disease modifying therapy to treat MS. The most common alternate diagnoses were headache (20%), spine spondylosis (11%), and white matter ischemic disease (11%). The diagnostic tests most likely to help differentiate MS from alternate diagnoses are recent imaging of the entire central nervous system and lumbar puncture.

**Conclusions:** This review highlights the importance of careful evaluation of a patient's presentation prior to diagnosing multiple sclerosis and also on receiving a referral for treatment options. Neurologists, and MS specialists especially, should re-evaluate an existing MS diagnosis given the high rate of misdiagnosis. Diseases misdiagnosed as MS vary but, concordant with some previous studies include headache, spine disease, and white matter ischemic disease.

#### Disclosure

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### MS Variants

#### EP1295

**Detailed characterization of pain and depression in NMOSD: prevalence, clinical features, management and impact on quality life**

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**Objective:** To evaluate prevalence of pain syndromes and depression as well as their effects on the activities of daily life (ADL) and quality of life (QoL) among patients with neuromyelitis optica spectrum disorder (NMOSD).

**Methods:** All NMOSD patients of one academic centre were contacted. Detailed characterisation of pain syndromes was done based on McGill, PainDetect and Brief Pain Inventory. Effects of symptomatic and immune therapies on pain severity were evaluated retrospectively. Using the Beck Depression Inventory (BDI), depression was classified into severe, moderate or minimal. QoL was evaluated with the SF-36 questionnaire.

**Results:** We achieved a high response rate of 93% (42 of 45 patients). 83% were female, the mean age was 44.1±12.4 years, 79% were antibody (ab)-seropositive: 26 AQP4-ab, 7 MOG-ab. The majority (79%) of patients reported NMOSD-associated pain

syndromes, 70% had neuropathic pain and 64% painful tonic spasms. The mean pain intensity was moderate (3.8±1.5, scale 0-10). Almost half of the pain sufferers (49%) had chronic pain. There were no differences between seronegative and seropositive patients, as well as between those with AQP4- and MOG-abs. 70% took pain relieving medications, however, they had still a pain intensity of 4.3±1.3 (scale 0-10). Among those with painful spasms, 33.3% only had antispastic medication. Tocilizumab was the only immune therapy with probable pain relieving effect: 3 of 4 patients reported improvement after a switch to tocilizumab. Pain syndromes were associated with a substantial reduction of ADL (4.1±2.0, scale 0-10) and the health related QoL (34.2 vs. 46.0 in pain free patients, p=0.015). Pain intensity significantly correlated with the following SF-36 items: physical and social role functioning, general health perception and bodily pain. 45% of patients had BDI scores indicative of depressive disorder (BDI>13), 32% of them moderate or severe (BDI>19). The BDI score was significantly higher in patients with chronic pain compared to episodic pain (15.1 vs. 8.1, p=0.02). Depressive disorder was clearly undertreated, only two patients, both with mild depression, took antidepressants.

**Conclusion:** Pain syndromes and depression are highly prevalent, undertreated and associated with reduced QoL and ADL in NMOSD. It is crucial for an adequate targeted therapy to differentiate between the following 3 pain patterns: neuropathic pain, painful tonic spasms and chronic pain associated with depression.

#### Disclosure

I.Ayzenberg has nothing to disclose

E.Henke has nothing to disclose

I.Kleiter has nothing to disclose

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#### EP1296

**Antinuclear antibodies as potential markers of disability and recurrence in patients with Neuromyelitis optica**

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**Background:** Neuromyelitis Optica (NMO) is associated with systemic autoimmune diseases and serological markers of non organ- specific autoimmunity. Clinical significance of autoantibodies in patients with NMO is still unclear, specially in patients with significant elevations of these autoantibodies and with no evidence of a rheumatic syndrome.

**Objective:** To determine the association among the presence of antinuclear antibodies and the number of episodes of transverse myelitis and optic neuritis in patients who have been diagnosed with NMO.

**Materials and methods:** The study was transversal, analytical, retrospective and homodemic, 187 records of patients with NMO were analyzed between 2009 and 2016, of those only 46 met inclusion criteria.

U de Mann Whitney and Spearman's Rho was used to determine the relationship between antibody titers and the number of episodes of optic neuritis, number of relapses of myelitis and the Expanded Disability Status Scale (EDSS).



**Results:** We found a statistically significant difference in the number of relapses between patients with positive and negative ANAs, being higher in the patients with ANAs positive ( $U = 85$ ,  $p = 0.000$  and  $U = 84$ ,  $p = 0.000$ ) respectively, both with a significance level of 5% (0.05).

A positive and statistically significant correlation was identified between ANAs titration with the EDSS score ( $r = 0.5632$ ,  $p = 0.001$ ).

**Conclusion:** The positive association between the severity of the disease and the presence of autoantibodies, which until now are not involved in the pathogenesis of the NMO, could suggest that these antibodies reflect the degree of inflammatory disease activity if this can be confirmed in subsequent studies, the autoantibodies particularly the ANAs could be a useful clinical prognostic tool.

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### EP1297

#### Maintenance therapeutic plasma exchange in patients with neuromyelitis optica spectrum disorders

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**Background:** Therapeutic plasma exchange (TPE) is performed for the treatment of severe neuromyelitis optica spectrum disorders (NMOSD) relapses, but the efficacy of maintenance TPE (mTPE) in NMOSD has been underreported so far.

**Material and methods:** Eighteen NMOSD patients (15 female, 3 male; median age, 46.3 years), were treated with mTPE, once monthly. In the group A ( $n=9$ ), mTPE was initiated after the treatment of severe relapse and performed until the maximal neurological recovery was achieved. In the group B ( $n=9$ ), mTPE was used as an add-on therapy to steroids and/or classical immunosuppressants, in cases of disease activity in spite of the optimal treatment (4 patients), or in addition to steroids in patients with a poor compliance, intolerance or contraindications for immunosuppressive therapy (5 patients). The Expanded Disability Status Scale (EDSS), including total EDSS score and functional systems scores, were used to assess the level of neurological disability before and after mTPE treatment. Annual relapse rate was used as a clinical disease activity marker.

**Results:** Median duration of mTPE treatment in the overall group of patients was 1.15 years (range 2.4 months–3.8 years). The EDSS score after the last mTPE procedure was significantly lower than before the first mTPE in the total group of patients ( $p < 0.001$ ), and also in the group A ( $p < 0.05$ ), while the EDSS score in the group B was unchanged during mTPE. The statistically significant improvements after mTPE were observed in pyramidal,

sensory and bowel/bladder scores. The average annual relapse rate was significantly lower during mTPE than before mTPE initiation in the total patient group ( $p < 0.001$ ), as well as in both subgroups A ( $p < 0.01$ ) and B ( $p < 0.05$ ).

**Conclusion:** Our results show that the use of mTPE as an add-on therapy is associated with the reduction of disease activity and/or with neurological improvement in patients with NMOSD.

### Disclosure

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J. Drulović serves on scientific advisory boards for Bayer Schering Pharma, Merck Serono, Teva, Genzyme, a Sanofi Company, Roche, and received honoraria for speaking from Merck Serono, Teva, Bayer Schering, Genzyme, a Sanofi Company, Medis; and has also received research grant support from the Ministry of Education and Science, Republic of Serbia (project no. 175031).

### EP1298

#### Clinical course and prognosis of neuromyelitis optica spectrum disorder in a Moroccan cohort

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**Background:** Neuromyelitis optica spectrum disorder (NMOSD) was suggested to have a more severe course in low and middle income countries, particularly among populations from North Africa.

**Objectives:** To describe the clinical course and prognosis of NMOSD in a Moroccan NMOSD population.

**Patients and methods:** A retrospective monocenter study was conducted. Patients from January 1999 to December 2015 fulfilling the 2015 International Consensus Criteria for NMOSD were included.

**Results:** Sixty four patients were included. Mean age at onset was  $35.7 \pm 10.7$  years, and the sex ratio was 1/3.56. Non transverse myelitis (NTM) was the initial clinical event in 29.4%, 17.2% presented with a Devic's syndrome and 15.6% with intractable hiccups nausea and vomiting syndrome. Half of patients had more NTM attacks than transverse myelitis. Brain lesions were found in 71.2%. Twenty four percents had associated autoimmune diseases. Approximately half of patients reached an EDSS score of 6

after a median disease duration of 5,7 years, and 18,8% had an EDSS less than 1,5 on follow up. Median progression index was 0,78 and median multiple sclerosis severity score was 8,64. Disease age of onset (HR 1,51 for each decade; 95% CI 1,08-2,11), myelitis (HR 2,72; 95% CI 1,05-7,05) or multifocal first clinical event (HR 3,34; 95% CI 1,20 - 9,35), ratio of NTM (HR 0,04; 95% CI 0,01-0,30) and being under disease-modifying therapy (HR 0,31; 95% CI 0,15-0,64) were the only factors associated with progression to an EDSS score of 6.

**Conclusion:** We could not find any study using the new criteria for NMOSD to study their prognosis. Hence, comparisons are difficult to make and conclusions difficult to draw. However, our patients seem to have a worse outcome, even with broad criteria that include subtypes of patients with a better prognosis.

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### EP1299

#### Is there any relation between tumefactive demyelinating lesions and antibodies against MOG and AQP4?

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**Background:** Tumefactive demyelinating lesion (TDL) is a rare form of demyelinating disorder, which recently has received more attention. TDL is defined as a demyelinating lesion larger than 2 cm. In most cases, although TDL represents a form of multiple sclerosis (MS), according to current knowledge TDL refers a heterogeneous group of inflammatory central nervous system demyelination. The pathogenesis of TDL is unknown. But, recent case reports demonstrated the presence of aquaporin 4 (AQP4) IgG in cases with TDLs.

**Objective:** To reveal if there is any relation between the occurrence of TDL and antibodies against myelin-oligodendrocyte glycoprotein (MOG) and AQP4.

**Methods:** All patients were seen in Istanbul University Cerrahpasa School of Medicine Neuroimmunology Unit. Twenty-four patients with TDL which larger than 2 cm were included. All serum samples were analyzed at Tohoku University. The cell-based assays (CBA) were used to test AQP4 and MOG antibodies.

**Results:** Most of the patients were female (17 female). The mean age of the patients was 34.26 (range: 16-56). The mean age at the time of first symptom was 27.66 (range: 11-40). No patients were receiving any treatment such as natalizumab or fingolimod during or before the development of TDL. The mean follow-up duration was 46.89 months. During follow-up, patients with TDL either converted to MS or didn't have any further attack. None of them diagnosed as neuromyelitis optica or Balo's concentric sclerosis. All patients with TDL were

found to be negative regarding to anti-aquaporin-4 IgG and anti MOG IgG.

**Conclusions:** Our study did not reveal any relation between TDL and the presence of antibodies against MOG and AQP4.

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### EP1300

#### Genetic polymorphism of aquaporin-4 gene in neuromyelitis optica spectrum disorder

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**Background and aim:** Neuromyelitis optica spectrum disorder (NMOSD) covers a variety of demyelinating autoimmune disorders of the central nervous system (CNS) caused by aquaporin 4 (AQP4) immunoreactivity at least in a subset of patients. Understanding the genetic polymorphisms of patients with NMOSD and other demyelinating disorders with resembling clinical phenotypes may disclose its pathogenesis. In this study, we genotyped AQP4 gene in patients with NMOSD, relapsing inflammatory optic neuropathy (RION), and optico-spinal multiple sclerosis (OSMS) and compared clinical and genetic features of these disorders.

**Methods:** We included patients with NMOSD, RION, OSMS, and healthy controls in our study. We collected demographic and clinical data of the patients and sequenced five exons of AQP4 gene using Sanger sequencing method.

**Results:** We recruited 35 NMOSD, 15 RION, 10 OSMS patients, and 30 healthy controls in our study. Of the patients, 48 (80%) were female and 12 (20%) were male. Age, gender, follow-up period, annualized relapse rate, and progression index were similar between the groups. Cerebrospinal fluid protein levels were higher in patients with NMOSD (NMOSD: 50.0±33.2 mg/dl, RION: 24.2±4.9 mg/dl, OSMS: 20.0±4.0 mg/dl; p=0.02). Oligoclonal band positivity in OSMS patients were more frequent compared to other groups (NMOSD: 12.0%, RION: 7.0%, OSMS: 80.0% p=0.01). Compared to healthy controls, there was no significant difference in the frequency of any AQP4 allele in patients with NMOSD and OSMS. On the other hand, we detected three new single nucleotide polymorphisms in patients with RION.

**Discussion:** Clinical and laboratory features of NMOSD suggest that it is a distinct disorder rather than a spectrum of diseases that covers RION and OSMS. Our study did not reveal any allelic difference in AQP4 gene in patients with NMOSD and OSMS, suggesting that polymorphisms of AQP4 gene are unlikely to confer NMOSD susceptibility.

## Disclosure

Nothing to disclose.

### EP1301

#### Neuromyelitis optica phenotype associated with anti-TNF therapy in psoriatic arthritis

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**Introduction:** To describe a case of intractable hiccup and vomiting, followed by new retrobulbar optic neuritis that presented within 8 years of adalimumab treatment initiation in a patient with psoriatic arthritis and prior optic neuritis 4 years ago.

**Methods:** This case was evaluated with visual field testing, brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and laboratory evaluation, and treated with intravenous methylprednisolone followed by plasmapheresis.

**Results:** A brain and orbital MRI showed T2-weighted hyperintensity of the postrema area and left optic nerve, this with gadolinium enhancement. CSF findings were 8 cells/ $\mu$ L, with normal protein and absence of oligoclonal IgG bands. Serum aquaporin-4 antibody was negative (analysed by cell-based assays with live transfected cells). Our patient made only a partial visual recovery and was subjected to treatment with Rituximab.

**Conclusion:** Optic neuritis is a potentially sight-threatening complication of anti-TNF therapy. This unusual case can suggest an additional association: lesion of postrema area and recurrence of severe optic neuritis, both considered spectrum of neuromyelitis optica's phenotype.

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### EP1302

#### Atypical multiple sclerosis and idiopathic inflammatory demyelinating diseases in a series of 74 consecutive cases

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**Objectives:** To classify patients with atypical MS findings and Idiopathic Inflammatory Demyelinating Diseases (IIDD).

**Background:** More and more cases have been recognized with atypical clinical or MR findings, suggesting atypical MS diagnosis or (IIDD).

**Material and methods:** Since 2007, we conducted a nationwide study to collect all the patients with atypical MS / IIDD. Patients have been categorized into 6 groups as previously described: cavity MS (defined by large area of hypointensities within high intensities on Flair sequences), solitary sclerosis (isolated lesion involving the upper cervical spinal cord / medulla junction), ADEM like lesions (defined by a first clinical episode with MRI showing extensive enhanced lesions by gadolinium injection), tumoral demyelinating lesion (TDL) (isolated lesion > 20 mm diameter of the white matter). Two other IIDD types are identified: "MS with normal brain MRI" type (defined by a persistent normal brain MRI despite clinical temporal and spatial dissemination) and "pseudo-leukodystrophy MS" (defined by symmetrical demyelinating lesions on the initial brain MRI).

**Results:** 74 patients met the inclusion criteria. Cavity MS consisted of 11 cases (F: 7 / M: 4, mean age of onset: 41.0, range: 30-52), characterized by a progressive course in 10/11 with a mean EDSS score of 6.4 (range 2-8). Solitary sclerosis included 4 cases (1F / 3M), mean age 32.3 (28-39), TDL group consisted of 25 cases (19F / 6M), mean age: 34.3 (18-65). During a mean follow-up of 70.1 (6-181) months, 36 % fulfilled McDonald 2010 MS criteria. 76% did not present any clinical relapse. Normal brain MR group consisted of 12 cases (F 9/M 3; mean age: 29.3yo, range: 12-46). All of them presented spatial and temporal dissemination, but none fulfilled Wingerchuk 2015 criteria for seronegative NMOSD. Initial symptoms included optic neuritis in 5, myelitis in 5 and brainstem related symptoms in 2. Pseudoleukodystrophy MS consisted of 10 cases (4F/6M, mean age: 35.0 yo, range: 16-47), with a progressive evolution in 7/10 of these cases and a mean EDSS score of 4.7 (range 0-9). ADEM group consists of 12 cases with multiple enhanced lesions. Careful analysis of the MRI led to objective a few lesions without gadolinium enhancement in 11/12. 9/12 presented occurrence of further relapses.

**Conclusions:** Spectrum of atypical MS and IIDD is enlarged in this series. These results lead to extend the previous classification of IIDD / atypical MS.

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### EP1303

#### Atypical myelitis of multiple sclerosis: description of a French cohort



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The “atypical” myelitis of multiple sclerosis (MS), are characterised by longitudinally extensive myelitis ( $\geq 3$  vertebral segments), transverse myelitis ( $> 50\%$  of spinal cord in the axial plane), or pseudovascular (anterior or central) cord lesions.

This study is observational, retrospective, multicentric, and includes incident cases between 2012 and 2017. Sixteen patients were included in the University Hospital of Strasbourg, Nice, Poitiers and Montpellier in France. We collected demographic information, clinical and radiological characteristics of myelitis, laboratory results including CSF, brain and spinal cord MRI, treatment, and clinical follow-up.

The aim of this study was to collect atypical cases of myelitis related to MS to better characterise this population.

All patients fulfilled 2010 Macdonald criteria without any other alternative diagnosis. The mean age of onset was 39,1  $\pm$  12,4 years, the sex ratio was 1,6 women for 1 man. The myelitis was the first relapse for 12 patients, the second for 2 patients and the third for 1 patient. The intrathecal synthesis of immunoglobulin was found in all cases. On spinal cord MRI, we observed 3 longitudinally extensive myelitis, 9 transverse myelitis, 3 transverse and longitudinally extensive myelitis and 3 patients have an association with a central cord lesion. The median EDSS was 4,75 [1-8] during the relapse, 4,5 [0-6,5] after 6 months and 3,5 [0-7] after 3,9  $\pm$  3,1 years of follow-up.

Myelitis occurred as a second relapse for 2 patients and 5 patients experienced a progressive course of the disease. The small size of our cohort is a consequence of the rarity of this clinical manifestation in MS. These atypical myelitis are the first relapse for 12 of 16 patients, it seems to be the starter of the pathology in this form. A better recovery than in the NMO spectrum disorders or systemic diseases seems to emerge at the beginning of the pathology but also a quicker evolution towards progressive form.

The atypical myelitis are not frequent in MS and seem to be an entity which have a medullary tropism, during the first relapse and the recurrences.

## Disclosure

Nothing to disclose

## Paediatric MS

### EP1304

#### Visual pathway changes in children with multiple sclerosis and acquired demyelinating disorders

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**Background:** Cross-sectional studies show structural and functional visual pathway changes in youth with acquired demyelinating syndromes (ADS).

**Objective:** To assess longitudinal structural and functional visual pathway changes in pediatric MS and monophasic ADS (mono-ADS), and to determine the relationship of sex to such changes.

**Methods:** Standard visual assessments including optical coherence tomography (OCT) (Cirrus HD-OCT) and visual function metrics (best corrected high-contrast and low-contrast letter acuity, color vision, visual field, visual evoked potentials) were collected prospectively (2010-2017) in children with MS and monoADS at variable intervals after incident demyelination and after clinical episodes of optic neuritis (ON), if any. Data acquired within 90 days from ON were excluded. Changes in structural and functional metrics were assessed using joint mixed multivariate longitudinal modeling. Results are reported for  $p < 0.05$ . No correction for multiple comparisons was performed given the exploratory nature of the study.

**Results:** We included 42 youth with MS (30f, mean follow-up (f-u) (SD) 1.4y (1.3)), and 41 with monoADS (23f, f-u 1.0y (1.3)). 38% MS and 43% monoADS had no episodes of ON. The first year *post* incident demyelination showed thinning of ganglion cell-inner plexiform layer (GCIPL) in males with MS (-25.4  $\mu\text{m}/\text{y}$ ) and retinal nerve fiber layer (RNFL) in females with MS (MSf) (-11.2  $\mu\text{m}/\text{y}$ ) and with monoADS (-9.8  $\mu\text{m}/\text{y}$ ). Thereafter, MSf showed milder, progressive RNFL and GCIPL thinning (-1.8  $\mu\text{m}/\text{y}$  and -2.1  $\mu\text{m}/\text{y}$ ). Greater RNFL and GCIPL thinning was seen with increasing ON episodes (avg. -5.5 and -5.3  $\mu\text{m}/\text{episode}$ ). MSf with no history of ON had progressive RNFL and GCIPL thinning in the first year *post* incident demyelination (RNFL -12.0  $\mu\text{m}/\text{y}$ ; GCIPL -9.7  $\mu\text{m}/\text{y}$ ) and afterwards (RNFL -1.7  $\mu\text{m}/\text{y}$ ). Analysis of functional metrics showed progressive worsening of color vision in MSf (-0.02%/y), which correlated with RNFL ( $R=0.6$ ) and GCIPL ( $R=0.4$ ) decreases over time. No significant longitudinal changes were detected in other functional metrics.

**Conclusions:** Longitudinal assessment suggests progressive thinning of RNFL and GCIPL in youth with MS, which correlate with changes in color vision, and are more pronounced in females and in the first year *post* incident demyelination. Our results, which are limited due to the small number of male participants, may point to sexual dimorphism in the mechanisms of visual pathway damage or repair in pediatric MS.

## Disclosure

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### EP1305

#### Gut microbiota function and relapse risk in pediatric multiple sclerosis (MS): using predictive metagenomics

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**Background:** Previous work suggests a role for the gut microbiota in relation to relapse risk in paediatric MS. However, little is known about which microbial metabolic pathways might be involved.

**Objective:** To explore the association between the predicted relative abundances of gut microbial genes encoding metabolic and related pathways and relapse risk.

**Methods:** Children  $\leq 18$  years old attending a University of California, San Francisco pediatric MS clinic were invited to participate. All met McDonald criteria and were within 2 years of onset. Stools were shipped on ice and stored at  $-80^{\circ}\text{C}$ . The 16S ribosomal RNA gene was amplified from extracted DNA and sequenced via the Illumina MiSeq platform. Predicted function was assessed via the validated Phylogenetic Reconstruction of Unobserved States algorithm mapped to the Kyoto Encyclopedia of Genes and Genomes pathways. Longitudinal follow-up post-stool sample ('baseline') was obtained by mixed methods; both prospectively and through retrospective chart review. Assessors were unaware of the gut microbiota profiles. Associations between 11 *a priori* selected pathways (based on the wider literature and categorized as 'high vs. low' [ $\leq$  vs.  $>$  median] relative abundance of inferred microbial genes), were assessed in relation to subsequent relapse risk using survival analyses. Cox models were adjusted for age and disease-modifying drug (DMD) use.

**Results:** 17 relapsing-remitting MS cases (10 girls) aged 12.5 years (mean) with a mean disease duration of 10.3 months (range 2-23) provided stool samples. Eight (47%) were DMD naïve. Over a subsequent follow-up of up to 41.6 months (mean=19.8 months), 7 relapsed. A shorter time to relapse was associated with a lower relative abundance of microbial genes related to tryptophan metabolism ( $p=0.011$ , log-rank test) and higher abundances for both biotin metabolism and flavonoid biosynthesis (both  $p=0.018$ ). After covariate adjustment for age and DMD exposure status, only flavonoid biosynthesis remained significant, although the 95% confidence intervals were wide (hazard ratio=20.3; 95%CI:1.3-315.9,  $p=0.032$ ).

**Conclusions:** Findings suggest that gut microbiota function may be associated with subsequent relapse risk. A high abundance of inferred microbial genes encoding flavonoid biosynthesis were associated with a shorter time to relapse relative to a child with low abundance. Further investigations are warranted.

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### EP1306

#### Physical activity and its association with white matter integrity and cognitive efficiency in pediatric-onset multiple sclerosis

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**Background:** The association of physical activity (PA) on white matter (WM) integrity and cognition has yet to be fully described in pediatric-onset MS patients.

**Objective:** To determine whether level of self-reported strenuous PA is associated with WM integrity and cognitive efficiency (CE) in pediatric-onset MS patients.

**Methods:** Participants included 24 pediatric-onset MS patients (mean age=18.45±2.76yrs; mean disease duration=53.39±32.30mths) recruited from the Hospital for Sick Children (Toronto, Canada). Healthy age-/sex-matched controls (HCs) were recruited from the community (N=34). Participants completed a neuropsychological test battery from which a CE composite score was derived by averaging the z-scores of two processing speed tasks (i.e. Symbol Digit Modalities Test [SDMT] and WJ-III Decision Speed). Self-reported strenuous PA was calculated based on the frequency of strenuous PA engaged in for more than 15 minutes per week. WM integrity was evaluated via diffusion tensor imaging (DTI), using tract-based spatial statistics (TBSS). DTI metrics (FA, AD, and RD) were extracted for the entire WM matter skeleton, and 26 specific tracts. Groups were compared via independent samples t-tests on CE, PA, and WM integrity. Pearson partial correlations (two-tailed, adjusted for age;  $\alpha=0.01$ ) were conducted to examine the association between white matter integrity, CE, and self-reported strenuous PA.

**Results:** Patients had significantly reduced WM integrity relative to healthy controls in 21 of 26 interrogated tracts ( $p < .01$ ). This was further exhibited by lower avg-FA, and higher avg-AD and avg-RD in the entire WM skeleton ( $p < .001$ ). CE z-scores did not differ between MS and HC, and fell in the age-expected range. Mean self-reported strenuous PA did not differ between groups (MS:2.66x/week; HC:2.96x/week). CE did not associate with indices of WM integrity or self-reported strenuous PA in either group. Self-reported strenuous PA also did not associate with WM integrity.

**Conclusion:** DTI metrics are sensitive to disease pathology in pediatric-onset MS. This study did not confirm that WM integrity is associated with CE; however, this cohort of MS patients was relatively cognitively preserved. While no association between self-reported strenuous PA and WM was observed, future controlled studies evaluating exercise interventions are required to determine whether the integrity of WM can be favorably improved in MS patients and positively impact cognition.

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Christine Till: Nothing to disclose

## EP1307

### Serum tryptophan is associated with paediatric multiple sclerosis onset and disease activity

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**Background:** Tryptophan (Trp) metabolites have been shown to modulate the immune response in EAE. We sought to determine if serum Trp levels are associated with the risk of MS or relapse rate in children with MS.

**Methods:** Paediatric-onset MS and clinically isolated syndrome (CIS) patients within 4 years of disease onset and controls < 22 years old were recruited at UCSF, a tertiary care center. Prospective relapse data after enrollment were used. Serum Trp was measured using liquid chromatography-mass spectrometry.

We extracted and amplified DNA from available stool samples (n=17) and performed 16S rRNA sequencing. We applied a validated algorithm to enable metagenomic predictions from this sequencing data, and drew inferences as to the potential functional capacity of the gut microbiota (PICRUSt; Phylogenetic Investigation of Communities by Reconstruction of Unobserved States).

Association between serum Trp level and disease risk was assessed by a logistic regression model, adjusted for age, sex and race/ethnicity. Negative binomial regression models adjusted for age, race/ethnicity, sex and disease-modifying therapies were used to assess the association between serum Trp levels and relapse rate. Association between relative abundance of microbial genes involved in Trp metabolism and time to relapse was assessed using Kaplan-Meier curves.

**Results:** Serum Trp was measured in 82 MS/CIS cases and 17 controls. The mean (standard deviation) of serum Trp level was 11.0 (2.3) mcg/ml in cases and 12.8 (2.7) mcg/ml in controls. Each 1 mg increase in serum Trp level decreased the odds of having MS by 24% (95% CI: 4% - 40%,  $p=0.024$ ). There was no association between serum Trp levels and relapse rate in male patients, while each 1 mcg/ml increase in serum Trp in female patients was associated with a 26% decreased in the relapse incidence rate ratio (IRR: 0.74, 95% CI: 57% - 97%,  $p=0.026$ ). Patients with a lower relative abundance of microbial genes involved in Trp catabolism had a shorter time to relapse during follow-up than those with higher abundance (log-rank test  $p=0.011$ ,  $\leq$  vs.  $>$  median relative abundance).

**Conclusion:** Higher serum Trp levels are associated with lower risk of developing MS in children and lower relapse rate in female patients with paediatric MS. Trp metabolism by gut microbiota may be involved in this process. Additional case and control samples are being tested.

## Disclosure

Authors report no potential conflict of interest related to this work.

## EP1308

### Epidemiological aspects of childhood MS in Iran

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**Introduction:** Childhood multiple sclerosis (early-onset multiple sclerosis) approximately incorporates 3-5% of the MS population. In this study we tried to investigate prevalence, incidence and epidemiological aspects of childhood MS in last decade in Fars, southern Iran.

**Patients and methods:** During a retrospective study between 2005 to 2016 all patients with childhood MS (onset before age 16) were enrolled in the study. Prevalence, Incidence, demographic data, primary clinical presentation and month of birth of all patients were collected via a data gathering form. Statistical analysis was performed under supervision of statistical specialist.

**Results:** In this duration overall 209 patients with childhood MS were diagnosed. Prevalence of Childhood MS was 4/24 (Per 100.000) and mean incidence in this duration was 0.85 (Per 100.000 in each year). The incidence rate increased significantly from 2005 to 2016 (P value < 0.01).

13.4% (28 Patients) were boys. Mean age of the patients at the time of diagnosis was 14.02 years ( $\pm 2.8$ ) (Range: 1 to 16 years). Mean age of diagnosis in boys was  $12.64 \pm 4.24$  and in girls was

$14.24 \pm 2.45$  years. The difference between the age of diagnosis in girls and boys was statistically significant. (P value: 0.005) Only 6% of patients had < 10 years in the time of diagnosis. Optic Neuritis was the most common initial presentation in our patients. (37%).

**Discussion:** Here we showed that Childhood MS in Iran is not a rare condition especially in the girls and the incidence rate increased recently. Nowadays, Prevalence is similar to the western countries. Clinical suspicious is very important for correct and early diagnosis.

**Keywords:** Childhood MS, Iran, Epidemiology

## Disclosure

There is no conflict of interest.

## EP1309

### CSF kappa free light chains in early-onset multiple sclerosis

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**Background:** Inflammatory patterns in cerebrospinal fluid (CSF) are fully evolved already at the first clinical manifestation of multiple sclerosis (MS), therefore CSF analysis may help considerably in establishing correct diagnosis in childhood or adolescence. CSF specific oligoclonal bands (OB) demonstrate comparable diagnostic sensitivity in early and adult-onset MS, however result is only qualitative and rater-dependent. Measurement of kappa free light chains (KFLC) could provide a faster and easier to standardize tool but was not yet performed in paediatric MS.

**Objective:** In our study we aimed to evaluate the diagnostic significance of CSF KFLC in paediatric MS.

**Methods:** CSF and serum samples of paediatric patients with MS ( $n = 18$ , 15 girls) and other non-inflammatory neurological disorders ( $n = 9$ , 5 girls) were analysed. Median age at the time of spinal tap was 16 years (range 13-17) in the MS group and 13 years (range 7-17) in controls who presented mainly with headache syndromes. KFLC concentrations were measured by nephelometry, using monoclonal antibody immunoassay. The presence of OB was determined with agarose isoelectric focusing followed by alkaline phosphatase immunoblotting.

**Results:** Eighty-nine percent of our MS patients had CSF specific oligoclonal bands. CSF KFLC concentrations were higher in MS patients with a median 2.7 mg/l (range 0.1 - 19.4 mg/l) compared to the controls median 0.1 mg/l (range 0 - 1.1 mg/l);  $p < .0001$ . Diagnostic sensitivity of CSF KFLC concentration was 83% if the cut-off 0.3 mg/l derived from our previous adult-onset MS data was used. Diagnostic specificity of OB was 100% and 89% for the

CSF KFLC concentration. CSF KFLC to total protein ratio, which roughly accounts for brain CSF barrier integrity, demonstrated the same diagnostic accuracy as KFLC concentration with a median 1.0% (range 0.02% - 5.5%) in young MS compared to 0.03% (range 0.02% - 0.26%) in the control group ( $p < .0001$ ).

**Conclusion:** Our results show the relevance of KFLC as a diagnostic biomarker in the early MS. Study in a larger paediatric cohort is needed to investigate the age-related differences in CSF concentrations and to elucidate characteristics in other demyelinating disorders. Quantitative differences in CSF KFLC levels among the young and adult onset MS patients may require adjustment of the optimal cut-off value.

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## EP1310

### Natalizumab treatment in pediatric multiple sclerosis patients does not affect pubertal and developmental genes

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**Background:** Natalizumab treatment in pediatric multiple sclerosis (MS) population has a good efficacy reducing relapse rate and disability progression. However, the effect of Natalizumab on children puberty and development is not fully covered.

**Objective:** To determine whether Natalizumab treatment affects the expression of age, gender and Tanner developmental stage related genes.

**Methods:** Peripheral blood mononuclear cells (PBMC) were obtained from pediatric MS patients at baseline and at one year of Natalizumab treatment. Gene expression microarray analysis using Affymetrix Inc. technology (HU-133A-2 microarrays) was performed. Transcriptional changes associated with Natalizumab treatment and patients' age, gender and Tanner developmental stages were analyzed by weighted gene co-expression network analysis (WGCNA) software. This method creates clusters of highly correlated genes which can be related to treatment and children developmental external traits. Biological functional analysis was performed by Ingenuity software.

**Results:** Gene expression data of 10 pediatric MS patients, 6 females, age  $13.9 \pm 0.6$  years, disease duration  $1.5 \pm 0.3$  years and Tanner scale measurements ranging from pre-adolescent to fully mature morphology, demonstrated a network of 722 coordinately changing genes organized in 3 WGCNA modules induced by Natalizumab treatment ( $p < 0.05$ ). This signature was associated with differentiation of pre-B-Cells ( $p = 3.05E-09$ ) and B-Cells ( $5.34E-07$ ), proliferation ( $p = 4.23E-06$ ) and expansion ( $p = 1.04E-04$ ) of B-Cells, similarly to Natalizumab molecular effects in adult MS patients. Age, gender and Tanner stage were associated with two modules each, all distinct from Natalizumab-induced modules. No significant correlations were found between



Natalizumab induced gene-modules and age, gender and Tanner stage related traits.

**Conclusion:** Natalizumab treatment in pediatric MS population does not affect pubertal and developmental genes.

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### EP1311

#### Five-year follow-up of pediatric onset Neuromyelitis Optica Spectrum Disorders (NMOSD)

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**Introduction:** NMOSD is an inflammatory central nervous system condition mediated by serum aquaporin-4 immunoglobulin G antibody (AQP4-IgG). After knowledge of importance AQP4 IgG new diagnostic criteria to adult NMOSD has been described. Pediatric onset NMOSD is rarely described and long-term follow up are missing. The present report aim to describe a long-term follow-up pediatric onset NMOSD using the International Panel of NMO Diagnosis (IPND) updated in 2015.

**Method:** We assessed all patients enrolled in our neuroimmunology service from January 2005 to April 2017 whose NMOSD symptoms began before 18 years-old and met the updated 2015-IPND diagnostic criteria.

**Results:** from 375 patients with NMOSD, 16 were pediatric cases (4,2%). There were 2/16 males, 4/16 caucasian and 12/16 of mixed ethnic background. Three patients had previous infectious disease. Two patients had other autoimmune conditions. Median age at onset was 11(6-18) years. Presenting symptoms were optic neuritis (9), myelitis (4) and acute brainstem syndrome (3). Median time to the second relapse was 6(1-36) months. Median annualized relapse rate was 1relapse/year. The main relapse syndromes were: optic neuritis (45), myelitis (36), brainstem (5), area postrema (2) and diencephalic (1). Eleven (68,8%) patients were AQP4-IgG positive. Thirteen patients had abnormalities in the cerebrospinal fluid but none had positive oligoclonal bands. MRI findings were compatible with NMOSD in all patients. No patient full field Mcdonald-2010 Multiple Sclerosis criteria. All patients were acutely treated with methylprednisolone, followed by plasmapheresis (8), cyclophosphamide (6) and immunoglobulin (3). The median relapse number prior to maintenance treatment introduction was 2(1-6). Patients were first treated with azathioprine

(14) or mycophenolate (2). Five patients switched azathioprine to mycophenolate (4) or rituximab (1), due to relapses. Median EDSS of 3.5(1-8) after 5(1-17) years of follow-up. Eleven patients had visual acuity less than 20/200 in the worst eye.

**Conclusion:** Our results confirm literature emphasizing optic neuritis as mainly inaugural presentation in pediatric NMOSD. This is the first long term follow up of pediatric NMOSD using 2015-IPND criteria showing a higher disability than previous report.

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### EP1313

#### Body Mass Index multiple sclerosis trajectories in paediatric

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**Background:** Obesity is a recognised risk factor for the development of paediatric multiple sclerosis (MS). Obesity is associated with an increase in pro-inflammatory adipokines and also contributes to vitamin D deficiency. The aim of this study was to assess the trajectories of body mass index (BMI) in paediatric MS patients both prior to and post MS-onset.

**Design and methods:** A retrospective chart assessment was completed on 27 paediatric MS subjects and 100 healthy controls. Height and weight trajectories were collected on paediatric MS subjects prior to, at, and post-MS diagnosis. Paediatric MS subjects were excluded if disease duration was less than 2 years at the time of data collection. In addition, clinical demographics (age of first symptom, race/ethnicity, age of puberty, and Expanded Disability Status Scores (EDSS)) were collected. BMI categories were classified by the Center for Disease Control (CDC) growth charts with dependence upon subject age and sex.

**Results:** Of the 27 paediatric MS subjects, 33% were of normal BMI, 41% were overweight, and 26% were obese at the time of the first symptom of MS. At 2 years post-diagnosis, 30% of subjects were of normal weight, 30% were overweight, and 40% were obese. Of subjects who transitioned BMI categories over 2 years: all obese subjects remained obese, 36% (n=4) of overweight subjects became obese, and 11% (n=1) of normal weight subjects became overweight. No subject transitioned to a lower BMI status within 2 years of disease onset.

**Conclusions:** Paediatric MS subjects have high rates of being overweight or obese at disease onset. Despite low EDSS scores



(all scores < 2.0), subjects of normal BMI at diagnosis tend to stay within a normal BMI range, whereas a third of our overweight subjects transitioned to obesity within 2 years of disease onset. Data analysis is ongoing for paediatric MS data prior to MS diagnosis in addition to the healthy control cohort.

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### EP1314

#### **Pediatric neuromyelitis optica is more severe than pediatric multiple sclerosis in Brazilian patients**

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**Introduction:** Recurrent demyelinating diseases during childhood are still a challenge. Pediatric multiple sclerosis (pMS) and neuromyelitis optica (pNMO) show some degree of overlapping but pNMO seems to be a more disabling disease. Randomized controlled clinical trials in children haven't been published to date. However, disease modified drugs (DMD) for MS and immunosuppressive agents for NMO remain the mainstay of the current treatment, based on the practice in adult patients.

**Objectives:** To evaluate the clinical and epidemiological features in patients with pediatric MS and NMO and compare both groups, in a Brazilian cohort.

**Methods:** Retrospective review of patients' files followed at the Neuroimmunology Clinic - Universidade Federal de São Paulo, Brazil, from 2005 to 2016, fulfilling the 2010 McDonald criteria for MS and the 2006 criteria for NMO with onset before 18 years. Statistical analysis was performed using chi-square, Fisher's exact test or Wilcoxon sign test when appropriate. The Kaplan-Meier method was used for estimating the time to reach EDSS 6. Data are presented as median and mean  $\pm$  standard deviation and significance was set at  $P \leq 0.05$ .

**Results:** Sixty-eight patients fulfilled the inclusion criteria for MS and 11 for NMO. The female:male ratio was 2,8:1 and 2,6:1 for MS and NMO, respectively. The mean ARR was 0.82 ( $\pm 0.8$ ) for MS and 1,5 ( $\pm 1.8$ ) for NMO; the mean PI was 0.31 ( $\pm 0.4$ ) for MS and 2.2 ( $\pm 4.2$ ) for NMO. Analyzing the number of relapses after and before the treatment with DMD for MS and azathioprine for NMO, both groups presented significant reduction in relapse rate. When comparing the groups, patients with NMO had higher EDSS on last appointment and they reached EDSS 6 earlier than those with MS.

**Discussion:** Pediatric demyelinating diseases in Brazil are similar to the diseases described in other countries with higher prevalence. Data suggests that NMO is more severe than MS in adults and this study shows that the same happens with pediatric patients. DMD treatment was effective in reduce relapse rate in MS and standard immunosuppression with azathioprine was effective in NMO. Treatment was well tolerated in both groups.

**Conclusion:** NMO is a more severe disease than MS in children. The treatment with DMD or azathioprine was safe and effective in the population analyzed.

### Disclosure

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### EP1315

#### **Educational outcomes in pediatric multiple sclerosis**

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**Background:** Cognitive impairment occurs in 30 to 50% of children and adolescents with multiple sclerosis (MS). The consequences of cognitive disability in adults with MS are well documented, however, little is known regarding the functional impact of cognitive impairment in children with MS. To our knowledge, no study has examined the concordance of performance on standard neuropsychological measures and academic achievement in children with MS.

**Objective:** To evaluate whether the Symbol Digit Modalities Test (SDMT), which is the most commonly used standard screening measure of cognition in MS, is related to academic achievement in a pilot sample of children and adolescents with MS.

**Methods:** Three metrics were used to assess academic performance in a small cohort of subjects with childhood-onset MS (n=11). General academic performance was quantified using grade point average (GPA), performance on a New York State standardized exam (Regents) and the Woodcock Johnson-III Test of Achievement (WJ-III; verbal and math subtests). The SDMT was also administered. All GPAs are reported on a scale out of 100. Normative scores were calculated for each test. Impairment was considered  $z \leq -1.5$  (SDMT),  $z \leq -1.5$  (WJ-III) and below a 65 on any Regents exam. A score of 65 is determined by New York State as the lowest score meeting competency in the associated subject area. Regents results were unavailable for two subjects.

**Results:** 10 of the 11 MS subjects were female, with a group mean age of 16.6 years ( $\pm 3.0$ ) and a mean grade level of 11.2 ( $\pm 2.8$ ). Mean overall GPA was 82.6 ( $\pm 12.4$ ). SDMT performance did not correspond well with academic performance. 8 participants had normal SDMT, of which 4 (50%) were impaired on at least one of two WJ-III categories (verbal and math). Of these 8 participants with normal SDMT, 3 (38%) scored below 65 on at least one Regents exam.

**Conclusions:** The SDMT, though a widely used screening measure for detection of cognitive impairment in pediatric MS, is not always concordant with academic achievement in this pilot sample. Future work in larger samples is needed to determine whether standard neuropsychological tests adequately capture/predict decrements in academic achievement in children with multiple sclerosis.

### Disclosure

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## EP1316

**Ocular flutter as presenting manifestation of pediatric multiple sclerosis with positive anti-MOG antibodies - a case report**

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**Introduction:** Ocular flutter is an opsoclonic disorder with rapid, low-amplitude horizontal saccadic oscillations without inter-saccadic intervals. It has been described in the context of infectious diseases, drug toxicity, or paraneoplastic syndromes. The neuro-anatomical region associated with ocular flutter has not been clearly defined. However, in a few cases, cerebellar or PPRF lesions have been reported. Ocular flutter has been described once in adult-onset Multiple Sclerosis (MS) during disease course. However, ocular flutter has never been reported as a presenting symptom of MS, particularly pediatric MS with positive anti-MOG antibodies.

**Case report:** We describe a 13 year-old girl who presented with a 5-day history of abnormal ocular movements with concomitant blurred vision and involuntary head movements. On neurological examination rapid, horizontal saccadic oscillations of low amplitude in association with mild cerebellar signs were found. Brain MRI revealed three periventricular and one subcortical non-enhancing lesion. Furthermore, oligoclonal bands and IgG index were negative. The atypical presentation and MRI findings not fulfilling Barkhof criteria led to an original diagnosis of "opsoclonus-myoclonus". The patient followed the protocol for malignancy and was treated with corticosteroids with good response. The search for neuroblastoma or other malignancy was negative. She remained free of symptoms for the next three years until she presented again with the same ocular oscillations without any other clinical manifestations. Brain MRI was repeated and lesions were now typical for MS. A second LP revealed oligoclonal bands in CSF. A diagnosis of MS was made. Further investigations included positive serum anti-MOG antibodies and negative antibodies to antigen of neural receptors and glial cells.

**Conclusions:** Ocular flutter is an extremely rare clinical manifestation of MS that can be the presenting feature of the disease. The presence of positive anti-MOG antibodies, which is found in a minority of pediatric MS cases, is a further interesting observation.

**Disclosure**

M. Breza reports no conflict of interest.  
 C. Kotsalis reports no conflict of interest.  
 N. Smyrni reports no conflict of interest.  
 G. Koutsis has received research grants from Genesis Pharma and Teva, consultation fees, advisory boards and honoraria from Genzyme, Genesis Pharma, Teva and Novartis  
 E. Anagnostou reports no conflict of interest.  
 J. Tzartos has shares in a diagnostic laboratory (Tzartos Neurodiagnostics) in Athens.

C. Kokkinis reports no conflict of interest.

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A. Papavasiliou reports no conflict of interest.

## EP1317

**Case studies of Rituximab in pediatric patients with multiple sclerosis**

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**Introduction:** Around 3-5 % of multiple sclerosis (MS) cases have their first attack during childhood. Some of these patients continue to suffer acute relapses and progression of disability despite initiating an appropriate treatment, hence, there is justified need to introduce new biological therapies in pediatric population. Rituximab [Mabthera (R), Roche, Basel, Switzerland] is a monoclonal antibody directed against the B cell marker CD20, and was found quite successful in treatment of MS in adults.

**Patients and methods:** We report four cases of pediatric patients with MS, who were treated with Rituximab. Clinical outcome as well as safety profile of treatment were assessed.

**Findings:** Median age at disease onset was 13.7 years. In all patients high number of the lesions was found in MRI. The treatment with Rituximab was initiated 3, 4, 8 or 36 months after disease onset (median age 14.8). In two cases Rituximab was the first line of the treatment due to rapid progression of disease in the clinical status and MRI images. In other case, despite application of intravenous immunoglobulin, another relapse occurred within one month and Rituximab was introduced. In the fourth case, both interferon beta-1b and glatiramer acetate were tested sequentially, however, none of them stopped progression of disease and consecutive attacks. Finally, Rituximab was administrated 3 years after MS onset. In three patients no progression of MS was found in MRI images one or two years after administration of Rituximab (500 mg in a single dose). In one case progression of MS was observed in MRI after three months. Because of deep depletion of B-lymphocytes in all patients, further doses of Rituximab were not administrated.

In three patients a stabilization of clinical status was achieved despite the initial rapid progression.

**Conclusions:** This case series indicates that Rituximab may be a promising and effective complement to currently established treatment of MS in pediatric patients not responding to conservative therapy. Further research is required.

**Disclosure**

Nothing to disclose

## EP1318

**Depression and physical performance in pediatric onset MS patients**

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**Objective:** To describe depression in Pediatric onset MS (POMS) patient and determine whether it associate with physical performance.

**Background:** POMS has been shown to lead to significant disability. Patient reported outcome (PRO) measures in POMS have been shown to be associated with disease duration in small series but require validation in longitudinal studies. We aim to determine association between depression and physical performance and potentially reduce disease progression.

**Design/methods:** POMS patient charts were reviewed for demographics, clinical characteristics, PRO and functional outcome (FO). Patients' demographics, FO and PRO were compared between nonslow and SG (if 7 or more seconds). Both 9 hole peg test (9HPT) and timed 25 foot walk (T25FW) were examined for its associations with clinical depression parameters.

**Results:** A total of 44 POMS patients' charts were reviewed, overall median (IQR) PHQ9 score was 4.0 (1 to 7), 38.6% was depressed Patient health questionnaire (PHQ9>4), 18.2% had T25FW 7 or higher and 37.5 % of the SG group required assistance with gait and 25% needed assistance with transfers. Both PHQ9 (Spearman  $r=0.46$ ,  $p=0.002$ ) and Euro Qol five dimension questionnaire (ED5Q) [ $r=-0.40$ ,  $p=0.07$ ] were moderately associated with T25FW, and EQ5D was moderately associated with both non-dominant ( $r=-0.43$ ) and dominant 9HPT ( $r=-0.32$ ). Age of onset, gender, and race and disease course was not associated with SG. In addition to older age (Median 33 vs. 21 years), longer disease duration (17.5 vs. 5.9 years) were found in SG group, PHQ9 (6.5 vs 3.0) was also higher in SG, 62.5% in SG and 33.3 in non-SG were depressed (PHQ9>4).

**Conclusions:** POMS patients commonly had both depression and gait disorder. In addition to age and disease duration which are not modifiable, modifiable psychological status may contribute to quality of life in POMS. POMS rehab may need to consider psychology treatment.

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## EP1319

### Longitudinal evaluation of cognitive, academic, and adaptive functioning in pediatric MS

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**Objective:** To assess changes in cognitive, academic, and adaptive functioning in pediatric onset multiple sclerosis (POMS). Studies demonstrate early weaknesses in attention and fine motor ability but investigations of functional outcomes including academic and adaptive functioning are limited.

**Methods:** 18 children/adolescents with POMS underwent initial and follow-up neuropsychological evaluations. Impairment was defined as > 1 standard deviation below published normative data. 72 percent were female. Ethnicity was 39% Hispanic, 28%

African American, 33% Caucasian. Mean age of onset was 12.6 years. Mean time from symptom onset to initial neuropsychological evaluation was  $1.36 \pm 1.2$  and  $3.2 \pm 1.2$  years at follow-up. Minimal physical disability accrued from initial evaluation (mean EDSS = .44) to follow-up (mean EDSS = .35). All received disease modifying therapy.

**Results:** Consistent with the literature, cognitive impairment rate was 33% initially and at follow-up. Mild impairments were noted in visual-motor integration (initial SS =  $80 \pm 16$ , follow-up SS =  $75 \pm 12$ ) and attention (initial T =  $61 \pm 30$ , follow-up T =  $62 \pm 17.6$ ).

Parents reported inattention (initial T =  $62 \pm 8$ ; follow-up T =  $64 \pm 6.2$ ) and lower adaptive functioning (initial SS =  $82 \pm 10$ , follow-up SS =  $81.9 \pm 12.5$ ).

Multiple regression analysis revealed that 86 percent of the variance in adaptive functioning was accounted by a model including self-report anxiety/depression, attention, and fine motor ability ( $F=6.4$ ,  $p=.04$ ).

**Conclusion:** Consistent with the literature, early weaknesses in attention and visual-motor ability were noted and remained stable. Academic functioning remained in the Average range, despite mild cognitive weaknesses and increased school absences. Adaptive functioning was below age-expected levels early and remained low at follow-up. Adaptive functioning was predicted by self-report of anxiety/depression, attention, and fine motor ability.

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## EP1320

### Characteristics of pediatric multiple sclerosis in the west of Algeria

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**Introduction:** Multiple sclerosis (MS) is a disease of young adults, but its onset in

Childhood is frequently observed. In recent years a number of Number of networks participated in advancing the management of this disease in the child.

**Objectives:** Describe the clinical, paraclinic characteristics of pediatric MS.

Appreciate the response to different treatments.

Describe the evolution and compare it to adult onset.

**Patients and methods:** Prospective and retrospective study of MS patients with baseline age less than 18 Years. The positive diagnosis was made according to McDonald's criteria. Cerebral and spinal cord was performed with cerebrospinal fluid study. Was appreciated by the EDSS. The substantive treatment was prescribed according to the clinical form.

**Results:** We collected 25 patients. The sex ratio (F / H) 3.3. Average starting range was

$15 \pm 4.38$  years. The mono symptomatic onset was the most frequent (76.6%).cerebral MRI showed hypersignals peri ventricular (91%), cerebellum and corpus callosum (38% and 36%). Interferons



were prescribed in 76%, Natalizumab in 9.5%. The recurrent-relapsing form was observed in 87.5%. The current EDSS of patients is between 4-6 in 28.5% and greater than 6 in 19%. The median time to reach EDSS 6 in our patients was 8.27 -10.68 years where as in the adult form it was 12.17 - 13.24 years.

**Conclusion:** During childhood MS, functional and cognitive dysfunction

Interferes with academic achievement. Start treatment as early as possible

Could improve the quality of life of young patients.

## Disclosure

No conflict of interest

## Natural course

### EP1321

**Risk of transition to secondary progressive multiple sclerosis and accumulation of disability in progressive multiple sclerosis are not influenced by current therapies**

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**Objective:** Current approved disease modifying therapies (DMTs) are effective to prevent relapses but are not effective to arrest the accumulation of disability once the progressive phase of MS (SPMS) have started. Phase III trials in relapsing-relapsing multiple sclerosis (RRMS) are not long enough to answer whether DMTs have an influence in reaching SPMS or in the long-term course of the disease. The objective of this study was to evaluate if current DMT are preventing the transition to SPMS or changing the evolution of the progressive phase of these patients.

**Methods:** RRMS patients later diagnosed of SPMS, followed in the MS Unit of two tertiary hospitals, (La Fe and Clinic, in Valencia, Spain), since the first relapse of the disease to the present, were selected. All patients received DMTs after a definitive diagnosis of RRMS. A second cohort of primary progressive multiple sclerosis (PPMS) patients were selected. Age at disease onset, type of DMTs administrated, basal EDSS, time to SPMS diagnosis and time to reach an EDSS of 3.0, 6.0, 8.0 and 10.0 was recorded. A comparison of the age and the time to reach a fixed disability for all groups was done by the Kaplan-Meier survival analysis. A Cox regression multivariate analysis in order to explore predictive variable of progression was realized.

**Results:** A total of 204 RRMS patients were selected and 77 (37.7%) of them were diagnosed of SPMS. A second cohort of 139 PPMS was selected, so a total of 217 progressive MS (PMS) were followed-up for a mean time of 16 years (sd 7.3). SPMS patients were all treated with first-line DMTs and 47 of them (61.0%) with second line therapy because of treatment failure. The mean time under treatment was of 12.9 years (sd 5.0). Progressive MS was initiated at a mean age of 42.7 year, without significant differences between PPMS and SPMS. Reaching an EDSS score of 3.0 in less time predicted a worse evolution in SPMS. Mean time to reach an EDSS score of 6.0, 8.0 and 10.0 was 8.8, 13.1 and 15.4 years respectively, without differences between SPMS and PPMS.

**Conclusion:** The course of progressive MS (SPMS and PPMS) is very homogeneous, independently of has received current treatments from first relapse in SPMS form. Treatment could prevent disability related to relapses but has a limited influence to prevent the transition to SP or to modify the posterior evolution.

## Disclosure

Carmen Alcalá: nothing to disclose

### EP1322

**The Bayesian Risk Estimate at Onset (BREMSO) correlates with cognitive and physical disability in patients with early multiple sclerosis**

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**Background and purpose:** Prevention of long-term disability is the goal of therapeutic intervention in relapsing remitting multiple sclerosis (RRMS). The Bayesian Risk Estimate for MS at Onset (BREMSO) was designed to give an individual risk score predicting disease evolution into Secondary Progressive MS (SPMS). The aim of this study is to investigate whether BREMSO correlates with physical disability, cognitive dysfunction, and regional brain atrophy during the early disease course.

**Method:** We investigated 100 patients with RRMS or clinically isolated syndrome (CIS) enrolled in the AUBMC Multiple Sclerosis Interdisciplinary Research (AMIR) study, with at least two years of follow-up and disease duration of less than six years. BREMSO score was calculated for all participants at disease onset. At each visit, cognitive function was assessed using the Symbol Digit Modalities Test (SDMT) and physical disability using the Multiple Sclerosis Severity Score (MSSS), Timed 25-Foot Walk Test (T25-FW) and 9-Hole Peg Test (9-HPT). Out of the 100 patients, 30 had a baseline MRI performed at the radiology department of the AUBMC. 3DT1 with gadolinium injection and 3D FLAIR images were acquired. The intra cranial volume (ICV) as well as the subcortical gray matter structures and the corpus callosum (CC) were automatically segmented and their volumes measured.

**Results:** The mean (SD) age was 28.1 (11.19) years, MSSS 3.17 (2.36) and disease duration was 2.4 (1.78) years. In multivariate linear regression analyses, controlling for age and education, the BREMSO score correlated negatively with SDMT at visit 1 ( $\beta = -0.33$   $p = 0.019$ ), visit 2 ( $\beta = -0.34$   $p = 0.017$ ), and visit 3 ( $\beta = -0.34$   $p = 0.014$ ). BREMSO correlated positively with MSSS at visit 1 ( $r = 0.38$ ,  $p = 0.006$ ), visit 2 ( $r = 0.47$ ,  $p < 0.0001$ ), and visit 3 ( $r = 0.42$ ,  $p = 0.002$ ), but did not correlate with T25-FW and 9-HPT. MRI results showed a negative correlation between the BREMSO score and the CC volume at baseline ( $p < 0.03$ ). No correlation was found between the BREMSO score and the intracranial volume and the subcortical gray matter structures volume. This can be due to the small sample size or short interval follow up.

**Conclusions:** The BREMSO score is directly correlated not just with the physical progression of the disease (MSSS) but also with the cognitive disability (SDMT and CC volume measurements) in early MS. Future studies might incorporate MRI measures into



the BREMSO score increasing the sensitivity and specificity of this score.

### Disclosure

All authors have no conflict of interest to disclose.

### EP1323

#### Prognostic value of cerebrospinal fluid kappa and lambda free light chains in clinically isolated syndrome in Argentina

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Cerebrospinal fluid (CSF) immunoglobulin free light chains (FLCs) have been suggested to provide prognostic information in clinically isolated syndrome (CIS). The objective of this study was to assess the prognostic value of FLCs in patients with CIS suggestive of multiple sclerosis (MS) in a group of patients from Buenos Aires, Argentina.

**Methods:** Paired CSF and serum samples from 36 patients presenting with CIS were collected between 2014 and 2017. CSF and serum kappa (K) and lambda (L) FLC concentrations were measured using the FLC immunoassay Freelite™ (The Binding Site, Birmingham, UK) on a SPAPLUS analyzer. Demographic and clinical data was recorded, and mainly included time between CIS diagnosis and conversion, and the degree of disability (determined by the EDSS scale). MRI at baseline and follow-up (every 12 months) was evaluated to determine the percent brain volume change (PBVC) as a measure of brain atrophy. FLC concentrations were compared in CIS-MS converters vs. CIS non-converters and expressed as median±SD and the correlation between FLC and PBVC was assessed by binary logistic and Cox regression analyses.

**Results:** A total of 36 patients were included, median age 37±4 years, median follow-up time 28 ±9 months, during which 22 (61.1 %) patients converted to MS. The median concentration of FLCs at CIS diagnosis was slightly higher in CIS-converters compared to non-converters, but this did not reach statistical significance (KFLC: 7±5.3 mg/L vs. 5±2.3 mg/L,  $p=0.11$ ; LFLC: 0.7±0.33 mg/L vs. 0.5±0.23 mg/L  $p=0.16$ ). A strong inverse correlation was observed between the concentration of K and LFLCs at diagnosis and the change in PBVC during follow-up ( $r=-0.72$  and  $r=-0.65$ , respectively).

**Conclusion:** FLC concentrations at CIS diagnosis were not significantly higher in CIS-converters compared to CIS non-converters, but patients with higher CSF FLC concentrations tended to have increased brain atrophy during follow-up.

### Disclosure

No funding

### EP1324

#### Prognostic factors related to the severity of multiple sclerosis in the Japanese population

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**Background:** We previously reported that the prevalence and incidence of multiple sclerosis (MS) in Tokachi province, northern Japan, have increased in the last 15 years; accordingly, there have been changes in the clinical characteristics of patients with MS.

**Objectives:** To clarify the prognostic factors of MS in the Japanese population in Tokachi province using data obtained from 4 epidemiologic studies in the last 15 years.

**Methods:** Beginning in 2001, we have conducted prevalence studies every five years in the Tokachi province of Japan containing relevant clinical data for all included patients. Poser's criteria were used for diagnosis of MS in the four studies. The Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Severity Score (MSSS) were used to evaluate disease severity and disability progression, respectively. In our 2016 survey, MS patients were divided into two groups: the mild progression group (MSSS < 3) and the non-mild progression group (MSSS > 3).

**Results:** The MS prevalence and female/male ratio in Tokachi province increased from 8.1/100,000 (95% confidence intervals [CI] 5.4-11.7) and 2.6 in 2001 to 18.6/100,000 (95% CI 14.3-23.8) and 3.6 in 2016, respectively. Conversely, mean/median EDSS decreased from 3.0/2.3 in 2001 to 2.3/1.0 in 2016, respectively. Our 2016 surveillance data revealed that the mild progression group received fewer treatments with disease-modifying drugs (DMDs) than the non-mild group (50% vs 85%,  $p<0.05$ ), although there was no significant difference in disease duration between groups. Based on the multivariate analysis of factors influencing the non-mild progression group, male gender (OR 19.0; 95% CI 2.8-128), older age (OR 1.18; 95% CI 1.06-1.31), and positivity for oligoclonal bands (OCBs) (OR 19.1; 95% CI 1.6-233) were associated with a higher risk of progression. Age at onset was not correlated with disease progression.

**Conclusions and relevance:** Lower rates of treatment with DMDs in the mild progression group suggest that some patients do not necessarily need DMDs for good MS prognosis. Our data obtained from all MS patients in this cohort demonstrate that gender, birth year, and OCBs may be candidate prognostic factors for MS in the population in northern Japan. The increasing prevalence of MS in younger female patients may result in an increased proportion of patients with mild MS regardless of the use of DMDs treatments in northern Japan.

### Disclosure

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### EP1325

#### Utilizing the topographical model of MS to identify leading indicators of progression

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**Objective:** To demonstrate how the topographical model of MS can depict early manifestations of progressive disease utilizing a longitudinal clinical cohort.

**Background:** The topographical model depicts the admixture of relapsing and progressive aspects of MS. Central to this model is the observation that progression recapitulates a patient's prior relapse symptoms and clinically reveals previously silent lesions, incrementally manifesting a patient's underlying "disease topography". Using this cohort, we have previously demonstrated protracted diagnostic uncertainty during the transition to SPMS. Earlier identification of progressive disease may have implications for patient care and trial design.

**Methods:** We examined a subgroup of 10 patients from our published longitudinal cohort who transitioned from RRMS to SPMS. Neurologic exams were analyzed from all MS relapses during the RRMS phase, at time of formal SPMS diagnosis, and at most recent clinical visit. Functional Systems (FS) affected, location/laterality, and extent of recovery were recorded. Given its prognostic significance, the pyramidal/motor system served as the target FS for assessment of laterality and severity of symptoms at relapse and SPMS timepoints. Each patient's clinical course was mapped using the topographical model disease simulation software.

**Results:** Our cohort was 80% female, aged 31.6±8.6 years at diagnosis, followed for an average of 23.8±8.8 years with a mean of 3.1 relapses prior to SPMS classification. Symptoms were categorized by topographical regions of the model (spinal cord/optic nerve, brainstem/cerebellum, cerebral hemispheres). 83.3±0.2% of acute relapse symptoms were present at the transition to SPMS, increasing to 91.0±0.2% at most recent visit. These data demonstrate a correlation between the topographical distribution of relapse symptoms and accumulated deficits from subsequent progression. Mapped in the topographical model, above-threshold progressive disease became apparent an average of 7.3 years (range 5-11) earlier than the diagnosis of SPMS was applied in practice.

**Conclusions:** We have demonstrated the model's utility in depicting patients' disease topography as the loci of clinical progression. We utilize the recapitulation hypothesis to identify leading indicators of progression in individual patients to allow for precise, early recognition of progressive disease. Future empirical refinement using large clinical cohorts is planned.

## Disclosure

SC. Krieger has received compensation for consulting and advisory board work with Acorda Therapeutics Inc.; Bayer; Biogen; EMD Serono (Merck & Co., Inc.); Genentech; Genzyme; Mallinckrodt; Novartis; and Teva Pharmaceutical Industries Ltd. and has given non-promotional lectures with Biogen.

K. Cook, and M. Fletcher are employees of Harrison and Star, LLC, a healthcare communications company, which provided services for this project on a pro bono basis.

BM. Laitman has nothing to disclose.

## EP1326

### Time to, and rate of secondary progression in patients with multiple sclerosis: results of a systematic search

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**Objectives:** A number of studies have previously described rates of conversion from relapsing remitting multiple sclerosis (RRMS) to secondary progressive multiple sclerosis (SPMS), and times to the onset of secondary progressive disease. However, a comprehensive review of all the available evidence base has not been undertaken. The objective of this review was to synthesize the evidence on disease progression in MS patients.

**Methods:** A systematic search was conducted on MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews using the OVID platform to identify the articles reporting clinical course of multiple sclerosis. Studies were included that described risk of, or time to, conversion from RRMS to SPMS, or from relapsing SPMS to non-relapsing SPMS.

**Results:** In total, 5482 articles were identified and of these, 92 articles reported findings relevant to progression to SPMS. Following an initial relapsing-remitting course, there is a gradual increase in the number of patients converting to SPMS, with around 25% progressing by 10 years, 50% by 20 years, and more than 75% by 30 years. Estimates for the time to SPMS onset had significant variation ranging from 5 to 41.8 years, with most studies reporting a mean age of approximately 40 years at conversion to SPMS. Earlier onset of MS is associated with longer time to secondary progression, but also with conversion at a younger age. Frequent relapses in the relapsing-remitting phase, particularly within the first 2 years, correlate with early progression to SPMS. No studies described conversion from RRMS to relapsing SPMS, or from relapsing SPMS to non-relapsing disease.

**Conclusions:** Although there are a large number of studies reporting data on progression from RRMS to SPMS but there is significant variation in the reported data. Further studies may be required to understand the transition between RRMS to relapsing SPMS, and from relapsing SPMS to non-relapsing disease.

## Disclosure

Jennie Medin is an employee of Novartis Pharma AG, Basel, Switzerland;

Vivek Khurana is an employee of Novartis Healthcare Private Limited, Hyderabad, India.

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## EP1327

### Paroxysmal and unusual symptoms as first clinical manifestation of multiple sclerosis do not indicate benign prognosis - the PaSiMS II study

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**Background:** Paroxysmal (PS) and unusual symptoms (US) account for approximately 1.6% of initial manifestations of

multiple sclerosis (MS) and have comparable conversion rates to clinically definite MS (CDMS) as classical bout onset symptoms (CS). However, long-term prognosis and clinical outcome of patients experiencing PS or US as first clinical manifestation are unclear.

**Methods:** Clinical, MRI and cerebrospinal fluid data were obtained retrospectively and patients presenting with PS or US were compared to patients with CS presentation.

**Results:** In a cohort of 532 relapsing onset MS patients followed for a mean period of 11.4 years (SD 3.6), 10 (1.9%) patients initially presented with PS/US. PS/US patients received disease modifying treatment (DMT) in a significantly smaller proportion immediately after the first clinical symptom (30% vs. 61.7%;  $p=0.021$ ) and during the observation period (60% vs. 83.5%;  $p=0.033$ ). In multivariate models correcting for sex, age at initial symptoms, complete remission of initial symptoms, total number of T2 and contrast-enhancing lesions, presence of oligoclonal bands and DMT exposure, PS/US were not associated with lower annualized relapse rate or lower EDSS over time.

**Conclusion:** In addition to a similar conversion rate to CDMS, patients presenting with PS/US at disease onset display very similar relapse and disability rates as patients with CS onset. Consequently, initial presentation with PS/US does not indicate benign or atypical MS, but requires DMT initiation based on the same criteria as in CS patients.

## Disclosure

GB has participated in meetings sponsored by Biogen, Merck Serono, Novartis, Genzyme and Teva Ratiopharm.

RE has participated in meetings sponsored by and received honoraria (lectures and consultations) from Biogen, Merck Serono and Teva Ratiopharm, has received grants for educational purposes from Biogen, Böhlinger Ingelheim, Merck Serono, Novartis Pharma GmbH, Ottobock and Teva Ratiopharm, and has received honoraria for acting as consultant for Teva Pharmaceuticals Europe. LMW has participated in meetings sponsored by Bayer and Stryker.

HH has participated in meetings sponsored by, received speaker honoraria or travel funding from Bayer Schering, Biogen, Merck Serono and Novartis, and received honoraria for acting as consultant for Teva Pharmaceuticals Europe.

MA received speaker honoraria from Novartis.

SW has participated in meetings sponsored by, received honoraria or travel funding from Biogen, Merck Serono, Novartis, Sanofi Genzyme, Teva Ratiopharm, Allergan, Ipsen Pharma and Roche. FDP has received speaking honoraria from Biogen-Idec and Sanofi-Aventis Austria.

MW reports no conflict of interest.

MR reports no conflict of interest.

FD has participated in meetings sponsored by or received honoraria for acting as an advisor/speaker for Bayer Healthcare, Biogen, Genzyme-Sanofi, Merck, Novartis Pharma, Roche and TEVA.

TB has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for MS: Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Ratiopharm, Roche, Sanofi Aventis, TEVA. His institution has received financial support in the past 12 months by unrestricted research grants (Biogen,

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## EP1328

### Clinical presentation of clinically isolated syndrome (CIS); a long term follow up study in Iranian patients

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**Introduction:** In this study we tried to describe the clinical presentation of the patients with CIS in southern Iran and their follow up in 10 years.

**Patients and method:** 143 patients with CIS (124 females and 19 males) were enrolled in the study. Demographic data, clinical presentation and MRI findings of the patients were collected and patients were followed for 10 years.

**Results:** The most common initial clinical presentation was optic neuritis (40.6%). After a mean follow-up of  $3.4 \pm 1.1$  years, 38/143 patients (26.6%) had converted to CDMS.

The mean age at diagnosis was lower in CIS patients who converted to MS (27.6 versus 29.4 years), but it was not statistically significant ( $p=0.23$ ).

The conversion rate to CDMS was 49.2% (30/61) for patients who had  $\geq 3$  Brain MRI lesions, but it was 9.8% (8/72) in patients who had  $3 <$  lesions (OR =8.95, 95% CI=3.69-21.7,  $p < 0.001$ ).

**Conclusion:** The conversion rate in this Iranian population was similar to Western countries. Also, this study confirms this concept that the number of MRI lesions at baseline can be used as strong predictors of CIS conversion to CDMS.

**Keywords:** Clinical Presentation, Iranian Population, Multiple Sclerosis, Clinically isolated syndrome

## Disclosure

There is no Conflict of interest.

## EP1329

### The effect of exclusive breastfeeding on postpartum multiple sclerosis relapses

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**Importance:** The rate of multiple sclerosis relapses increases after giving birth. Making decision between starting breastfeeding or disease modifying drugs are difficult for most patients.

**Objective:** To assess if exclusive breastfeeding could reduce the risk of postpartum relapse.

**Design:** 66 women with relapsing remitting multiple sclerosis became pregnant during the years 2010-2013 were enrolled in our



prospective study .27 patients were excluded because of spontaneous abortion. 39 pregnant patients with the mean age of 30.6+<sub>-</sub>5.1 were closely followed up in each trimester and 3,6,12,24 and 36 months after delivery. Disease-modifying drugs were terminated in all patients. The effect of exclusive breastfeeding ( no supplemental feeding for at least 3 months) was compared on the first postpartum MS relapse with non exclusive breastfeeding(partial or no breast feeding at all), using Cox proportional hazards regression model.

**Results:** Out of 39 patients with full term delivery 27 (69.2%) were intended to exclusively breastfeed for at least 3 months and 12 (30.9%) did not breastfeed at all (25.8%)or included supplemental feeding(5.1%). Relapse did not occur during pregnancy. For those who did not exclusively breastfeed, the chance of experiencing at least one relapse during the first 6 months postpartum was 21.66 times(hazard ratio: 21.66, CL: 2.65-177.01, p=0.004). During the 36 months follow up, those who did not exclusively breastfeed were as almost as 2.45 times as likely to have at least one relapse in comparison to those patients who had exclusively breastfeed. (hazard ratio: 2.541 CL: 1.19-5.40 p=0.015)

**Conclusion:** In our sample, the women with multiple sclerosis could benefit from exclusive breastfeeding in order to significantly reduce the rate of postpartum relapses. Encouraging these women to exclusively breastfeed could be regarded as one of the modalities of treatment and a better approach to the disease.

## Disclosure

Navideh Sahebi: nothing to disclose  
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Kurosh Gharagozli: nothing to disclose

## Epidemiology

### EP1330

#### The incidence of cognitive impairment among Hungarian relapsing-remitting multiple sclerosis patients

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**Introduction:** Multiple Sclerosis (MS) frequently causes cognitive impairment aside from somatic symptoms, its prevalence ranging from 43-70%. Despite its frequency, there is very little data on its incidence, and none, utilizing the BICAMS screening battery.

The aim of our study was to determine the incidence of cognitive impairment among patients with relapsing-remitting (R-R) MS and clinically isolated syndrome (CIS) and assess possible predicting factors.

**Patients and methods:** We followed-up 242 R-R MS and CIS patients after 1 year, treated at the Department of Neurology of the University of Szeged and at the Jahn Ferenc Dél-Pest Hospital of

Budapest from the originally recruited 553 patients. We used the BICAMS battery to assess their cognitive state. For statistical analysis, we used logistic regression analysis, Chi-square and Fisher exact tests. We calculated the incidence rate.

**Results:** The mean age of our patients was 45.5±11.3 years, the mean age at disease onset was 31.3±9.8 years, the mean disease duration was 15.2±7.6 years and the median EDSS score was 2 points (range:0-6.0). Of the 243 patients, 62 were men and 180 women (man-women ratio was 1:2.9).

At baseline, 110 of the 242 patients were cognitively preserved. At the time of the follow-up, 25 patients developed some level of cognitive impairment (22.7%), the incidence rate was 103/1000 person-years. We found no significant predictor of developing CI with regression analysis. There was no significant difference between the genders, yet the proportion of male patients was higher (31% against 21%; p>0.05).

**Discussion:** At a 1 year follow-up, we found the incidence of cognitive impairment to be 103/1000 person-years among our patient group, which is in accordance to a previous report from Italy after a longer follow-up. We found no significant difference between the genders (unlike in our prevalence investigation), yet the proportions were slightly higher among males, so the lack of significance may be due to the relatively low number of male patients. We found no significant predictor of developing CI in this short follow-up period.

## Disclosure

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Zita Burány: nothing to disclose.  
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### EP1331

#### The prevalence of multiple sclerosis in the Province of Padua, North-East Italy, is significantly higher in urban areas and associates with air quality

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**Background:** The incidence and prevalence of Multiple Sclerosis have progressively and quite linearly increased in the Province of Padua, North-East Italy, over the last 5 decades. The cause(s) of this epidemiological trend are unknown. The role of environmental factors has to be considered.

**Aims:** To analyse the distribution of MS cases in the territory of Padua's Province and its association with residential locality types and local environmental features.

**Methods:** 1419 MS patients born and living in the province of Padua were included in the study. The following environmental parameters were considered: the residential locality type, the chemical composition of soil and the air quality (i.e., particulate matter < 2.5).

Based on the 2011 National Italian Territory classification, the province surface was classified in four different locality types: urban areas (789,233 inhabitants), isolated villages (50,570 inhabitants), productivity places (1,875 inhabitants) and countryside (79,683 inhabitants). Each patient's address was labelled according to such territorial classification. Furthermore, the urban domain of Padua was considered as an additional locality type.

**Results:** In the urban areas, MS prevalence was much higher (162/100,000) compared to isolated villages (109/100,000) or rural domains (98/100,000,  $p < 0.0001$ ). Moreover, when the city of Padua was separately considered, the prevalence significantly increased to 195/100,000 ( $p < 0.00001$ ). No association could be demonstrated with the content of selected metals (Cr, Co and Ni) in the soil. Three classes of air quality were used for grading the urban zones and their inhabitants (19.4-21.8, 21.8-23.0, 23.0-24.7 micrograms/cubic meter, annual average 1998-2015). Interestingly, the MS prevalence closely follows the three classes of air particulate (137, 165 and 193/100,000, respectively;  $p < 0.001$ ).

**Discussion:** Our findings suggest that the prevalence of MS associates with the residential type locality. Moreover, in the urban areas (the most impacted by the disease) a further increment of the risk associates with air quality. These observation indicates that environmental factors play a major role in the increased MS prevalence in the Province of Padua, North-East Italy, that rose from 16/100,000 in the early '70ies to 182/100,000 in 2017.

## Disclosure

Tateo Fabio and Grassivaro Francesca have nothing to disclose. Puthenparampil Marco received travel grant from Novartis, Sanofi-Genzyme, Biogen Idec, Almirall, Teva and Sanofi Aventis and honoraria from Almirall; he has been consultant for Genzyme Federle Lisa has received funding for travel from Novartis, Merck Serono, Biogen Idec, Sanofi-Genzyme, Bayer Schering Pharma, Almirall, Teva and honoraria from MerckSerono, Teva and Almirall. Miente Silvia received travel grant from Biogen Idec, Novartis, Sanofi Aventis and Teva Zito Antonio has nothing to disclose. Erica Stropparo has nothing to disclose. Cazzola Chiara has nothing to disclose. Toffanin Elisabetta has nothing to disclose. Ruggiero Susanna has nothing to disclose. Mario Ermani has nothing to disclose. Francesca Grassivaro has nothing to disclose. Davide Poggiali received travel grant from Biogen Idec, Novartis, Sanofi Aventis and Teva. Rinaldi Francesca serves as an advisory board member of Biogen-Idec and has received funding for travel and speaker honoraria from Merck Serono, Biogen Idec, Sanofi-Aventis, Teva and Bayer Schering Pharma. Perini Paola has received funding for travel and speaker honoraria from Merck Serono, Biogen Idec, Sanofi-Aventis, and Bayer Schering Pharma and has been consultant for Merck Serono, Biogen Idec and Teva; Gallo Paolo has been a consultant for Bayer Schering, Biogen Idec, Genzyme, Merck Serono and Novartis; has received funding for travel and speaker honoraria from Merck-Serono, Biogen Idec, Sanofi-Aventis, Novartis Pharma and Bayer-Schering Pharma, Teva; has received research support from Bayer, Biogen Idec/Elan, MerckSerono, Genzyme and Teva; and has received

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## EP1332

### Autoimmune diseases in multiplex MS families in the Netherlands

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**Background and objective:** Clustering of autoimmune diseases (AIDs) has been described in individuals with multiple sclerosis (MS) and their first-degree family members. However to what extent MS and other AIDs co-occur in MS multiplex families with two or more affected individuals is still controversial. We aimed to evaluate co-existing AIDs in MS patients and their first-degree family members from the Dutch MS multiplex families and compare them to spousal controls.

**Methods:** A total of 155 multiplex families (155 MS probands, 789 first-degree relatives and 212 spouses) were characterized for a history of 11 AIDs by means of a self-administered questionnaire.

**Results:** An AID was reported in 17 (11%) MS probands. In 67 (43.2%) MS multiplex families at least one AID was present in the first-degree relatives. Overall frequency of AIDs was similar in MS probands (11%), their first-degree family members (11%) and in spousal controls (5.2%). After correction for age at inclusion and gender, the odd ratios (OR) for AIDs were not significant for MS probands compared to spouses (OR=1.8, 0.77-4.34,  $p=0.17$ ), and for first-degree family members compared to spouses (OR=2.0, 0.98-4.10,  $p=0.06$ ). Frequency of AIDs in mothers of MS index cases was more than twice of that in fathers (19% vs 8%,  $p=0.0052$ ). Maternal second-degree relatives reported more often a presence of AIDs than paternal second-degree relatives (23% vs 10%,  $p=0.0020$ ).

**Conclusion:** Although nearly half of the Dutch MS multiplex families reported an AID, no excess of AIDs was present in MS patients from multiplex families or their first degree family members compared to their spouses. Increased autoimmunity in mothers and maternal relatives of MS index cases suggest that there might be a maternal parent-of-origin effect for AID in MS patients from multiplex families.

## Disclosure

JY Mescheriakova reports no disclosures.

RQ Hintzen reports no disclosures.

## EP1333

### Rising prevalence of multiple sclerosis in Mexico: a new estimation based on a multicenter registry and sanitary administrative data

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**Background:** Prevalence of multiple sclerosis (MS) in Mexico has been previously estimated between 10 and 15 per 100,000 inhabitants. With increasing mortality and hospitalizations associated to MS diagnosis in recent years, there have been insights about the possible rise in MS prevalence explaining this epidemiologic behavior.

**Objective:** To estimate MS prevalence in Mexico.

**Methods:** We first used information of a regional multicenter registry of Northeastern Mexico conducted during 2014. For the prevalence estimation we analyzed data of individuals pertaining to a captive State workers population covered by three regional hospitals (ISSSTE; *Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado*). Weighted mean prevalence (WMP) was calculated using information of individual institutions and 95% uncertainty intervals (95% UIs) are provided. WMP was validated with official National death certificates and hospital discharges databases for 2014 assuming a rate of 10.5 hospitalizations per 100 person-years and mortality of 2.5 per 100,00 MS patients. WMP estimate was considered reliable if UIs included the point estimations based on administrative databases provided by the National Health Information System.

**Results:** Of 641 patients included in the registry, we analyzed data of 140 individuals pertaining to a total population of 563,214 State workers covered by three regional ISSSTE hospitals. WMP was 23.67 per 100,000 inhabitants (95% UI: 15.86-35.31 per 100,00 inhabitants). In the remaining 501 individuals pertaining to hospitals covering non-captive population (i.e., floating population without constant insurance coverage) prevalence ranged from 3.59-9.88 per 100,000 inhabitants. Estimates based on hospitalizations and mortality of the whole Nation fell within the UIs WMP range (29.70 and 18.89 per 100,000 inhabitants, respectively).

**Conclusion:** The prevalence of MS in Mexico is 24 per 100,000 inhabitants. This new estimate may reflect a transition to a better diagnosis and a higher awareness within the community. However, we cannot completely rule-out a true increasing prevalence of MS in Mexico.

## Disclosure

Dr. Erwin Chiquete has received research grants from Sanofi and Ferrer Grupo; has served as research advisor for Sanofi, Novartis and Genzyme; and has received speaker honoraria from Novartis Mexico, Genzyme and Ferrer Grupo.

None of the other authors have relevant conflicts of interest to declare.

## EP1334

### Temporal trend in the disease activity of multiple sclerosis in Korea

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**Background and goals:** Epidemiologic studies have suggested an increasing temporal trend in the prevalence of multiple sclerosis (MS) across Asian countries. Nevertheless, the temporal trend in the disease activity of MS in these countries has not been fully evaluated yet.

**Methods:** One hundred seventy seven MS patients according to the international panel criteria

(112 females, mean age at onset of  $30.7 \pm 8.2$  years) were retrospectively included from four MS-referral hospitals in Korea. The T2 lesion burden in brain MRI at disease onset was analyzed and clinical outcome after disease modifying treatment (DMT) was examined. The positive rate of oligoclonal band (OCB) by isoelectric focusing (IEF) method and the frequency of IgG index more than 0.67 were investigated for each birth year group.

**Results:** From the 1950s to the 1990s, the number of patients born in each decade was 4, 25, 65, 67, and 16, respectively. Patients born in more recent decade had a significantly higher number of T2 lesions ( $\beta=0.614$  lesion per each year; 95% CI: 0.153-1.075;  $p=0.010$ ) at disease onset. The birth year was a significant risk factor for relapses within 1 year and within 2 years after initiation of DMT ( $p=0.020$  and  $p=0.001$ , respectively). The risk of clinical relapse within 2 years after DMT was 1.513 times higher when the birth year was delayed by 10 years (95% CI: 1.179-1.941;  $p=0.001$ ). Onset age did not show a significant difference in terms of relapse risk. The positive rate of OCB and the proportion of raised IgG index  $> 0.67$  tended to be higher in whom belong to a patient group of later born ( $p<0.001$  and  $p=0.003$ , respectively).

**Conclusions:** Our data imply that the disease activity of adult-onset MS patients in Korea is increasing over last five decades in terms of radiological and prognostic aspects. In addition, the patterns of CSF biomarkers have also been changing over time. This is a preliminary result from four MS-referral hospitals and further nationwide study is in progress.

## Disclosure

H.-J. Shin, W. Kim, S.-H. Baek, B.-J. Kim, J.-W. Hyun, S.-H. Kim, and S.-M. Kim have nothing to disclose.

H.J. Kim has lectured, consulted, and received honoraria from Bayer Schering Pharma, Biogen, Genzyme, HanAll BioPharma, MedImmune, Merck Serono, Novartis, Teva-Handok, and UCB; received a grant from the Ministry of Science, ICT and Future Planning; and accepted research funding from Genzyme, Kael-GemVax, Merck Serono, Teva-Handok, and UCB; serves on a steering committee for MedImmune; is a co-editor for the Multiple Sclerosis Journal - Experimental, Translational, and Clinical, and an associated editor for the Journal of Clinical Neurology.



## EP1335

**Disease-modifying therapies use in relapsing-onset multiple sclerosis patients in real-life settings in France: data from the OFSEP database over the period 1996 - 2017**

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**Background:** Beta interferon, first disease-modifying therapy (DMT) for multiple sclerosis (MS), was approved in France in 1996. Twenty years later, 12 medications are available, improving the therapeutic arsenal regarding acceptance and tolerability (injectable, oral and infused medications) but first of all efficacy, despite potential adverse effects. Approval of natalizumab in 2007 and oral first-line treatments in 2014 were major steps in the therapeutic strategy. Increased availability of DMTs associated with better knowledge of their efficacy and their risks had consequences on therapeutic decisions made by neurologists in daily practice.

**Objectives:** To describe use of DMTs in relapsing-onset MS patients in France over the last 20 years, the therapeutic sequences and switches; to assess impact of the arrival of new drugs on the practices; to search for a period effect in DMTs use.

**Methods:** This national observational cohort study was based on data collected through the 'Observatoire Français de la Sclérose en Plaques' (OFSEP), the French MS registry that included more than 54,000 MS patients in December 2016. All patients with a relapsing-onset MS and alive in 1996 (to get a chance to be treated) were included. All treatments (including off-label drugs) were considered, whatever their duration. Treated patients were described, as well as the DMTs prescribed (type, dates and reasons of stopping) and all the potential switches (considering place in the strategy as well as way of administration). Analysis was done globally (and will be done by periods: before 1996, 1996-2007, 2007-2014, since 2014).

**Results:** As a whole, 41,952 patients were included; 30,341 (72.3%) received at least one DMT, accounting for a total of 73,012 DMT initiations over a mean ( $\pm$ SD) follow-up duration of 13.6 $\pm$ 10.7 years from MS onset. First DMT was initiated after mean disease duration of 6.1 $\pm$ 7.2 years and the cumulative treatment duration was 6.3 $\pm$ 5.3 years, i.e. 49% of the follow-up duration. Injectable, oral, infused medications and off-label drugs concerned respectively 54.3%, 13.3%, 12.8% and 19.6% of DMTs. The most frequent switches were within first-line DMTs (n=10,874; 8,438 switches within injectable drugs and 1,837 switches from injectable to oral drugs), first to second-line DMTs (n=5,688), and within off-label drugs (n=1,918).

**Conclusion:** The OFSEP cohort offers the opportunity to describe therapeutic practices in France and their changes over time.

**Disclosure**

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## EP1336

**Familial multiple Sclerosis: a Portuguese hospital-based cohort study**

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**Introduction:** Little is known about familial Multiple Sclerosis (MS). It seems that MS appears earlier in familial forms with an anticipation of age from older generations to younger ones within a family. In this study we characterize the familial MS cohort from our hospital and compare clinical and imaging findings with non-familial patients.

**Methods:** From 656 MS patients, 31 (4.7%) presented one or more relatives with the disease

(11 families). We compared this group (1) with 66 age and sex-matched patients with non-familial MS (group 2), regarding: subtype, age of onset, time from onset to diagnosis, initial syndrome and Expanded Disability Status Scale (EDSS) score, Multiple Sclerosis Severity Score (MSSS) and first Magnetic Resonance Imaging (MRI) data. In group 1 we also analysed MS age of onset between different generations. In the statistic analyses, significant differences were considered for  $p < .05$  and marginally significant for  $p < .10$ .

**Results:** The female/male ratio was 2:1 in both groups, the mean age of onset was 31.2 and 34.5 years in groups 1 and 2, respectively, the most common subtype of MS was relapsing-remitting (group 1, 83.9%; group 2, 77.3%); these differences were not significant. The time between onset and diagnosis was similar in both groups (2-3 years) and sensory symptoms were the most frequent onset complains. For familial cases, the most common form of

kinship was between first degree relatives: siblings (38.7%) and parent-child (22.6%). A marginally significant difference was found when testing for anticipation of disease in younger vs. older generation ( $p=0.066$ ). Initial EDSS was significantly lower for familiar cases ( $p=.024$ ) while no differences were found in MSSS. At initial MRI, the group 1 had significantly less infratentorial involvement ( $p=.013$ ) and less contrast enhancing lesions ( $p=.019$ ).

**Discussion:** As reported in the literature, our study's familiar cases had younger age at onset than sporadic MS, although this difference didn't reach statistical significance. As reported by others, there seems to be a propensity of anticipation of MS and a milder initial disability in familiar cases. However no differences were observed in MSSS or progression to Secondary Progressive form between groups. We also found a milder lesion burden at initial MRI. If this is part of a genetic contribute or if family cases are more aware of MS symptoms leading to an earlier diagnosis, is still an intriguing question.

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### EP1337

#### Computer-based registry for central nervous system demyelinating disease in Brazil - REDONE databank

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**Background:** The inflammatory Central Nervous System disorders include multiple sclerosis (MS), optic neuromyelitis (NMO), acute disseminated encephalomyelitis (ADEM), and other demyelinating syndromes. Genetic and ambient factors may be different across the Brazilian regions, given the different rates of European, African and Amerindian ancestry and environmental factors in a continental country. However, no study has evaluated the possibility of an electronic registry in Brazil to generate relevant epidemiological information on autoimmune neurological diseases.

**Methods:** This pilot study included 67 neurologists distributed across all regions from Brazil whom have been granted access during the first quarter of 2016 to the Neuroimmunology module from the Brazilian Registry for Neurological Disorders (BRA-REDONE) sponsored by the Brazilian Academy of Neurology.

**Results:** During a 3 months period (1Q2016), half of the neurologists logged-in to the system. The distribution of registered members in the different Brazilian regions was: North 5.9%, Midwest 11.8%; Southeast 47%, Federal District 8.8%, and South 26.5%. From these, 25% (8/34) have successfully included more than 830 patients into the database.

**Conclusions:** In a very short period of time, we registered a large number of patients from all regions using a computer-based tool, indicating the feasibility and utility of such databases for large countries such as Brazil. These early results may provide data to establish incidence and prevalence across the Brazil regions with potential use in the promotion of public health policies.

### Disclosure

Doralina G. Brum: Nothing to disclose

### EP1338

#### Neuromyelitis optica spectrum disorder in Tehran, Iran

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**Background:** Neuromyelitis optica is an infrequent demyelinating disease and epidemiological information on NMO is rare. The aim of this study was to estimate the prevalence, clinical features and serology of NMO in Caucasian population in Tehran, Iran.

**Method:** A cross sectional study was performed during 2015 to 2016 in Tehran among patients registered with NMO diagnosis based on international 2015 consensus criteria in Sina hospital a tertiary care referral center in Tehran. A structured questionnaire was design in MS Research Center of Tehran university of medical sciences to measure the baseline characteristic, severity of symptoms and significant epidemiological variables which were associated for NMO.

The goals of study were described for 103 registered patients and data were collected from hospital database registry system and patient's information through face to face interview.

The logistic regression was applying in analysis by software package SPSS.

**Result:** The prevalence of NMO in Tehran was 0.86 per 100,000 in 2016 with point prevalence for females and males rate of 1.35 and 0.26 per 100,000 respectively.

Female to male ratio was 5:1. The mean age at the disease onset was 31.54 years old. NMO-IgG was positive in 44 (46.8%) and first presenting symptoms among patients were TM 29 (28.2%), ON in (23.3%), (17.47%) had unilateral declined visual acuity, TM + ON in (46.6%) and 2 (1.9%) of them presented NMO with other appearances. Based on our study, ON had significant association with female gender.

The adjusted odds ratio for sex was estimated for depression (OR = 6.83; 95% CI: 1.47, 31.71), migraine (OR = 1.27; 95% CI: 1.13, 1.42) and hypothyroidism (OR = 1.25; 95% CI: 1.12, 1.39).

**Conclusions:** We indicated that the risk of NMO is significantly higher among females and younger age group and patients who had background of depression, migraine and hypothyroidism.

### Disclosure

**Funding Source:** This study was funded by Tehran University of medical sciences.

**Conflict of Interest:** Authors declare no conflict of interest.

Although this study (the largest population based study) provides important current epidemiological data and we believe that our results provide crude minimum estimate rates of prevalence then are expected to rise dramatically in future studies. The outcomes of this study examined some significant epidemiological factors and clinical features for NMO. We indicated that the risk of NMO is significantly higher among females, younger age and patients who had history of depression, migraine and hypo toroid.

### EP1339

#### Characteristics and therapeutic management of patients with relapsing-remitting multiple sclerosis - data from a French multiple sclerosis population-based registry (the Multiple Sclerosis Registry in Lorraine Region)

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**Background:** New disease-modifying treatments (DMTs) approved since 2006 have probably changed the management of multiple sclerosis (MS) patients in current medical practice. However, few recent data are available on real-life therapeutic strategies implemented in MS patients.

**Objective:** To describe the characteristics and therapeutic management of MS patients since January 2007, using a French regional MS population-based registry (Registre Lorrain des Scléroses en Plaques, ReLSEP).

**Methods:** Data from patients with confirmed MS, first MS symptoms between 2000 and 2014, at least one medical consultation with a neurologist between 2007 and 2015, and without combined DMTs during at least 3 months were extracted from the ReLSEP database. Following descriptive results focused on patients with relapsing-remitting MS (RRMS).

**Results:** From the 6090 MS patients registered in the ReLSEP database, 1926 MS patients met all the predefined selection criteria, including 1663 RRMS patients at initial diagnosis (86%). Among these 1663 RRMS patients, 1483 patients (89%) received at least one DMT from diagnosis and 180 patients (11%) never received any DMTs. The characteristics of non-treated and treated patients were respectively as follows: women (73% and 76%), mean age at first MS symptoms (36±10 and 31±10 years), mean irreversible score on the Disability Status Scale (DSS, 1.4±0.8 and 1.2±0.5), and median patients' follow-up duration [9 years (Q1-Q3: 5-13) and 9 years (Q1-Q3: 5-12)]. Among the 1483 RRMS patients with at least one DMT from diagnosis, 507 patients (34%) from the 943 registered before 2007 started first DMT before this date (interferons and assimilated products 96%; non-selective IV (2%) and oral (2%) immunosuppressants). The other patients (n=976, 66%) received first DMT after January 2007: interferons and assimilated products (83%), oral Nrf2 pathway activators

(6%) oral selective immunomodulatory (4%), humanized monoclonal antibody anti-alpha-4 integrin (3%), non-selective IV (1%) and oral (1%) immunosuppressants, and oral selective immunosuppressants (1%).

**Conclusions:** Despite recent approval of new DMTs for MS, interferons and assimilated products remain the standard treatment for RRMS patients of the ReLSEP population. The proportion of RRMS patients treated with oral DMTs increased over time. However, a substantial proportion of RRMS patients (11%) never received any DMTs over the 9-year follow-up period from MS diagnosis.

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B. Tehard, L. Bitoun, Dr PH. Depoortere are employed by Roche.

### EP1340

#### Prevalence of multiple sclerosis in Quito, Ecuador

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**Background:** Ecuador has a low prevalence of multiple sclerosis (MS). An epidemiological study conducted 10 years ago showed that the prevalence of MS in Ecuador was 1.2 / 100,000 and in the city of Quito (latitude 0) 5 / 100,000 inhabitants. Since 2007 no new epidemiological studies have been carried out and we do not know if the prevalence has increased like it has in other regions of the world.

**Objectives:** To determine the prevalence of multiple sclerosis in the population of Quito and to describe its epidemiological characteristics.

**Methods:** We performed a retrospective descriptive study from January 1, 2014 to December 31, 2016. Patients included in the study were those who met the McDonald 2010 criteria for MS and lived in the city Quito for at least one year. Patients come from three third-level hospitals; Carlos Andrade Marín, Eugenio Espejo and Militar, which are institutions of national reference for diagnosis and treatment of MS. Patients who did not live in Quito were excluded from the study.

**Results:** We identified a total of 101 patients with MS, with a prevalence of 4.51 / 100,000 (CI 95%, 3.63-5.39). The average age was 41.85 years old (SD +/- 12.38). 66% of the cases were women; The female to male ratio was 2: 1. Eighty-two percent of the cases were relapsing-remitting MS, 9% clinically isolated syndrome, and 9% progressive MS. The mean EDSS was 3.18 (SD +/- 2.05).



**Conclusions:** The prevalence of MS in the city of Quito is low and is similar to that reported 10 years ago. The disease was more frequent in women. The present study has limitations due the fact that it is not a community study and it is imperative to create a surveillance system that allows us to obtain a better patient registry.

### Disclosure

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### EP1341

#### **$\alpha$ -Linolenic acid (ALA) serum levels are associated with reduced MRI activity in a prospective cohort of MS patients**

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**Background:** The omega-3 fatty acid  $\alpha$ -Linolenic acid (ALA) has anti-inflammatory properties, and consumption of food rich in ALA has been associated with a decreased risk of developing multiple sclerosis (MS) (1). It is, however, not known if serum levels of ALA affect disease activity in MS- patients.

**Objective:** To study whether disease activity is associated with ALA serum levels in patients with relapsing-remitting MS.

**Methods:** We conducted a prospective cohort study of 87 patients with relapsing-remitting MS, originally included in a randomized placebo-controlled trial (RCT) of omega-3 fatty acids in MS (the OFAMS Study), and followed them for two years with repeated MRI- and serum measures. The patients received no immunomodulatory treatment during the first six months, and all patients were initiated on subcutaneous interferon  $\beta$ -1a (IFNB) after month 6 and throughout the follow-up period.

MRI and serum ALA measurements were performed at baseline and at months 6, 12 and 24. We used random-intercept logistic regression to estimate the effect of ALA on disease activity adjusting for age and EDSS at baseline, treatment allocation in the RCT and IFNB-status. In a second multivariable model, we additionally adjusted for vitamin D, cotinine, HLA-DRB1\*15, vitamin A and BMI.

**Results:** Higher serum levels were inversely correlated with MRI disease activity. Each weight percent increase in ALA of total serum phospholipid fatty acid levels were associated with a subsequent reduced risk of new MRI-activity: OR 0.52 (95% CI:

0.29-0.95) for new T2-lesions, OR 0.68 (95% CI: 0.40-1.17) for new T1Gd+ lesions and OR 0.53 (95% CI: 0.28-0.97) for combined unique activity (the sum of T1Gd+ and new or enlarging T2 lesions). Similar Associations were found after further adjusting for HLA-DRB1\*15 status, vitamin D, cotinine, vitamin A and BMI.

**Conclusions:** We detected an inverse association between serum levels of ALA and MRI-disease activity. The association remained similar after adjusting for all several known cofounders. This indicates that ALA could have unique anti-inflammatory properties relevant for the pathogenesis of MS.

### References

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### Disclosure

Ø. Torkildsen served on the scientific advisory board for Biogen, Sanofi-Aventis, Merck.

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### EP1342

#### **Late onset multiple sclerosis**

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**Introduction and objectives:** Multiple sclerosis (MS) typically debut between the age of 20 and 40; however, the first symptoms can occur after age 50 and is classified as late-onset MS (LOMS). The purpose of the present study was to review the prevalence, presentation, and clinical characteristics of late-onset MS.

**Methods:** In this retrospective study what we include 450 patients with the diagnosis of MS established according to Poser or McDonald criteria, select those older than 50 years and review demographic characteristics, first onset symptom, diagnostic delay, disability at the time of diagnosis (EDSS), Progression Index (PI) disease course and findings in CSF, and MRI studies.

**Results:** We included 21 patients with LOMS (4,7%), of the total 450 MS patients, diagnosed between 1982 and 2016. 15 (71%) females and 6 (29%) males. Mean age at onset was 53(SD±3,4).

The most frequent first symptoms were motor deficits (52%), followed by brainstem disorder (24%), and sensory deficits (10%). The clinical course was in 42% relapsing-remitting (RR), in 38% primary progressive (PP) and in 19% secondary progressive (SP). The initial EDSS score was 3.7 (SD  $\pm 1.8$ ). The mean PI was 0.48. The mean of diagnostic delay was 52 months. The brain MRI has  $\geq$  nine lesions in 86%, and spine MRI has  $\geq$  three lesions in 52%. IgG oligoclonal bands were positive in 71% of patients in the CSF study. In addition 5 out of 21 (31%) patients had suffered a major depressive episode and 44% had cognitive impairment. In six cases there was a previous wrong diagnosis, being the most frequent the spondyloarthritic cervical myelopathy.

**Conclusions:** The onset of multiple sclerosis (LOMS) after age 50 is infrequent, in our series the most common type is RR but PP is more frequent than in another younger groups and motor symptoms are the most frequent initial neurological presentation.

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Jose E. Meca Lallana: nothing to disclose

### EP1343

#### Comorbidity prevalence in a multiple sclerosis center

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**Objectives:** Comorbidity is an area of increasing interest in multiple sclerosis (MS) and may have adverse impacts on MS course causing greater disability progression and influencing treatment choices and treatment outcomes. Our aims were to characterize the comorbidities of the MS center of Bergamo.

**Materials and methods:** We retrospectively evaluated the clinical history of 601 consecutive patients afferent to our MS center in 2016. We reported all comorbidities which could be relevant to health care utilization and could influence treatment choices in MS patients.

**Results:** Overall we evaluated the data of 487 patients with relapsing remitting MS, 103 patients with secondary progressive MS and 11 patients with primary progressive MS. 67% of our cohort were females and 33% were males. Mean age was 43.9 years old (SD 11.7). Median EDSS was 2.0 (range 1.0-9.0). 42.2% of patients had at least one comorbidity (28.2% only one comorbidity, 14.0% two or more comorbidities). Overall, at least one comorbidity was already present at diagnosis in 8.8% of our sample; 33.4% of subjects developed at least one comorbidity during MS disease course. 9.8% of our patients were affected by hypertension, 5.8% by dyslipidemia, 2.3% by diabetes, 2.8% by cardiac diseases, 4.7% by malignant tumors (21.4% breast cancer, 25.0% genito-urinary tumors, 7.1% gastrointestinal tumors, 3.6% lung cancer, 32.1% skin cancers, 10.8% other tumors), 20% by

psychiatric disorders (86.6% anxiety-depressive disorder, 13.4% psychosis or bipolar disorder) and 9.7% by autoimmune diseases (64.7% autoimmune thyroiditis, 9.8% psoriasis, 7.8% celiac disease, 17.7% other mixed autoimmune diseases). Diabetes and autoimmune disorders were equally detected before and after MS diagnosis, while the remaining comorbidities onset was more frequent during MS disease course.

**Discussion and conclusions:** We reviewed the prevalence of comorbidities in a single MS center. The high prevalence of comorbidities in our cohort underlines the complexity of MS patients, which is not confined to MS direct complications. A high rate of subjects developed comorbidities after diagnosis. An adequate prevention and a prompt management of comorbidities during MS disease course is essential and might be the key to ameliorate the health care utilization, prevent serious adverse events during MS treatment and obtain better clinical outcomes.

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### EP1344

#### Prevalence of multiple sclerosis in San Vicente del Raspeig, Spain: a population-based study

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**Background and objectives:** Available epidemiological data suggest that the prevalence of multiple sclerosis (MS) in Spain is progressively increasing during the last four decades. The aim of this study was to estimate the actual prevalence rate of MS in the southeast of Spain.

**Methods:** This epidemiologic study was conducted in the city of San Vicente del Raspeig, located in the southeast of Spain, latitude 38° 23', with a population of 56,715. April 10, 2017 was selected as the prevalence day. Case ascertainment included computerized primary care medical records system, the MS database of Alicante General Hospital, the district hospital that offers specialized care to MS patients and data from the MS patients' association. 2010 McDonald's criteria were used for the diagnosis of multiple sclerosis. Lublin criteria (2013 revisions) were used for MS phenotypes.

**Results:** A total of 58 patients (45 women, 13 men) had a confirmed diagnosis (Poser and 2010 McDonald's criteria). The overall crude prevalence rate was 102.3/100,000 (95% CI 79.1-132.2), 157.1/100,000 (95% CI 117.5-210.2) in women and 46.3/100,000 (95% CI 27.1-79.2) in men. Women/men ratio was 3.5. Mean age was 44.7 $\pm$ 11.1 years, 45.4 $\pm$ 11.2 in women and 42.3 $\pm$ 10.9 in men. A total of 45 of the 58 patients (77.6%) were treated with disease

specific therapies: glatiramer (13.8%), beta-interferon (17.2%), dimethyl-fumarate (17.2%), rituximab/ocrelizumab (12%), fingolimod (8.6%), natalizumab (6.9%), azathioprine (1.7%). MS phenotypes (2013 revisions) were: relapsing remitting MS (RRMS) with activity, 10.3%; RRMS without activity, 6.9%; secondary progressive MS (SPMS) with progression but without activity, 3.4%; SPMS without progression or activity, 6.9%; primary progressive MS (PPMS) without activity or progression, 3.4%; PPMS with activity and progression, 3.4%; PPMS with progression but without activity, 3.4%.

**Conclusions:** Our study suggests that the prevalence rate of MS and the women to men ratio is increasing in the southeast of Spain. The revised Lublin criteria for the clinical course gives a more dynamic description of MS phenotypes and should be included in epidemiological studies of MS.

### Disclosure

Natalia Perez-Carmona has received speaker honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, and Teva. Leticia Berenguer-Ruiz has received speaker honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, and Teva. Cristina Borrego-Honrubia: nothing to disclose. Ramon Gomez-Illan: nothing to disclose. Rosa Garcia-Tercero: nothing to disclose. Angel P Sempere has received compensation for serving on scientific advisory boards or in speaker's bureaus from Biogen Idec, Bayer Schering Pharma, Merck Serono, Novartis, Roche, Sanofi-Aventis, and Teva.

### EP1345

**Baseline characteristics from the COMBAT-MS study: Initial analyses suggest main driver for therapy choice is geographic location**

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**Background:** Novel disease-modifying therapies (DMTs) for multiple sclerosis (MS) have greatly improved treatment of the disease. However, real world data on long-term safety, tolerability, and comparative effectiveness, are still scarce. COMBAT-MS (COMparison Between All immunoTherapies for Multiple Sclerosis, EudraCT 2016-003587-39) is a Swedish, nationwide, long-term, prospective cohort study, including all patients with relapsing-remitting MS (RRMS), starting a first DMT or switching DMT for the first time, between 1st Jan 2011 and 30th June 2018, at any of Sweden's University Clinics. This corresponds to approximately 50% of the nationwide, eligible population. The primary objective of this study is to compare rituximab (RTX) with other MS-approved DMTs, regarding long-term safety and comparative effectiveness.

**Methods:** Current patients fulfilling the inclusion criteria were identified through the nationwide Swedish MS registry (SMSreg). For these patients, already registered data in the SMSreg,

regarding disease history, disease status, treatments, relapses, and imaging, were validated by medical-chart review. These initial patients, together with future patients also fulfilling the inclusion criteria, are followed with annual, structured follow-up visits, for a minimum of three years after enrolment.

**Results:** A total of 3626 patients fulfilling inclusion criteria were identified through the SMSreg and included in the medical-chart review. Primary analyses of baseline characteristics for these patients suggest that geographic location (centre) is the main factor driving channelling to either RTX or another DMT. However, patients starting RTX at inclusion were in general a few years older (median 38 vs 35 years [ $p < 0.001$ ]), had had the disease a few months longer (median 17 vs 13 months [ $p = 0.023$ ]), and had a slightly higher EDSS at the start of therapy (median 2 vs. 1.5 [ $p = 0.001$ ]), compared to all other therapies. Prospective follow-up began in June 2017.

**Conclusions:** Primary analysis suggest that the main driver for treatment choice is geographic location, rather than patient characteristics. However, some differences in characteristics were still observed and will have to be taken into consideration in future observational comparisons between RTX and other DMTs.

### Disclosure

The Combat-MS study is funded through a Patient-Centered Outcomes Research Institute (PCORI) Award (MS-1511-33196). PA, TF, AS, MG: Nothing to disclose.

JL has received travel support and/or lecture honoraria from Bayer Schering Pharma, Biogen, Novartis, Teva and Sanofi Genzyme; has served on scientific advisory boards for Almirall, Teva, Biogen, Novartis and Sanofi Genzyme; serves on the editorial board of the *Acta Neurologica Scandinavica*; has received unconditional research grants from Biogen, Novartis and Teva.

PN has received travel support from Bayer Schering Pharma, Merck Serono, Biogen and Sanofi Genzyme, honoraria for lectures and advisory boards from Merck Serono and Sanofi Genzyme, advisory boards for Novartis and Roche, lectures for Biogen and has received unrestricted grants from Biogen.

JB has received travel support and/or lecture honoraria from Almirall, Biogen, Sanofi Genzyme, Hospira and Merck Serono; has received unconditional research grants from Biogen and Merck Serono.

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KF has received an unrestricted academic research grant from Biogen and compensation for lectures from Biogen and Novartis, which have been exclusively used to support research activities.

ALG receives funding from NIH, National MS Society and PCORI. She was the site PI for 2 industry-sponsored phase 3 MS RCTs (Biogen-Idec, Roche).

MV has received unrestricted research grants from Novartis and lecture honoraria from Genzyme and for advisory boards from Roche and Novartis.

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### EP1346

**Characterization of the Hispanic male multiple sclerosis patient in Puerto Rico**

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**Background:** Multiple Sclerosis (MS) affects women more often than men. It is reported that MS is more aggressive in non-Caucasian men. The Puerto Rico MS (PRMS) Registry reported the highest incidence and prevalence among other Hispanic population.

**Objective:** Describe the Hispanic male MS patient in Puerto Rico (HMMS-PR).

**Methods:** Data was collected from the PRMS registry of newly diagnosed patients for the period 2013-2016. Data was analyzed using descriptive statistics.

**Results:** Out of 633 evaluated patients 159(25.12%) were male. Average age at onset was 33.4 and at diagnosis were 38.9. The time lag between symptom onset and diagnosis showed that 73.74% of patients were diagnosed within 0-5 years of their first symptom, 21.21% were diagnosed within 6-15 years, 3.03% were diagnosed within 16-25 years, and 2.02% within 26-31 years. The most common initial symptom was a sensory symptom (53.92%), followed by visual (40.20%), and then motor (32.35%). One fourth of the HMMS were disabled. 68.33% had EDSS scores from 0-3.0, 28.33% had a score of 3.5-6.0, and 3.33% had an EDSS score from 6.5-9. Vitamin D was also evaluated and it was shown that 65.22% of these patients had deficient/insufficient levels. 62.37% of patients had no smoking history and only 14.0% had a blood relative with MS. Hypertension, hyperlipidemia, and diabetes was seen in 17.82%, 6.93%, and 5.94% of patients respectively.

**Conclusion:** Our results show that HMMS-PR patients in this sample do not present a more aggressive MS presentation as was previously believed. The majority of the newly diagnosed male cases have an EDSS score below 3.0, which suggests that these individuals have low level of disability at diagnosis. The most common first symptom among newly diagnosed HMMS patients is a sensory symptom, followed by a visual and motor symptom. The time lag to diagnosis is in concordance with previously calculated number (4.1 years) and is similar to female patients. Vitamin D levels were found to be insufficient/deficient on most HMMS patients further validating the belief that it is a risk factor for MS. This study helps elucidate MS disease course in HMMS. Also, it shows that there is need to characterize more ethnic specific prognostic factors for MS patients since these non-Caucasian male patients do not depict a more severe MS presentation. Comparing these results to other MS male ethnic groups could help define racial differences among male MS patients.

## Disclosure

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Ivonne Vicente, Cristina Rubi, Ana Rivera, Guillermo Garcia, Astrid K Diaz: Have nothing to disclose.

## EP1347

### Bayesian spatio-temporal mapping of multiple sclerosis (MS) incidence ratio in Fars province, southern Iran

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**Background:** Multiple Sclerosis (MS) is an autoimmune disease of nervous System which affects young adults, especially young females. This study aimed to assess the geographical distribution of MS in Fars province in southern Iran using the spatial methods. Fars Province is one of the largest provinces in Iran which has a population of 4.6 million people.

**Patients and methods:** A total number of 5,868 patients diagnosed with MS according to the McDonald's criteria during 1990-2016 in Fars Province. Demographic and case-related information was obtained from the Iran MS Society (IMSS), Shiraz office database. Overall Fars Province has 29 counties. We used Bayesian spatial and Bayesian spatio-temporal models to study relative risk and trend of MS incidence in the Province and each county separately.

**Results:** Out of 5,868 registered MS patients, 82% were female. County-level crude incidence ratio ranged from 0.31 to 9 cases per 100,000 populations. The highest smoothed SIR (1.80) was in the Shiraz County in the center of Fars province, while the lowest smoothed SIR (0.11) was in the Zarindasht County in southern Fars. Moreover, there is an increase trend in MS incidence but very smooth.

**Conclusion:** Here we analyzed the geographical distribution of MS in part of Iran, to obtain a reliable map of disease incidence. This map may help us to identify the possible cluster and localize the risk areas. This epidemiologic approach may help us to find any possible underlying environmental causes of MS in Iran.

**Keywords:** Bayesian Spatio-temporal, BYM model, Multiple sclerosis, Incidence

## Disclosure

There is no conflict of interest.

## EP1348

### Incidence and prevalence of multiple sclerosis in Saint Petersburg

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**Introduction:** Multiple sclerosis is characterized by a non-homogeneous distribution around the world. There are no system epidemiological data for multiple sclerosis (MS) in Saint-Petersburg.

**Objective:** To calculate the incidence and the prevalence of multiple sclerosis (MS) in Saint-Petersburg (located in North-West region of Russia).

**Methods:** This is an observational, cross-sectional, descriptive study. The City Center of MS was founded in October 2011. This is the first center in Russia conducting electronic health records, which allowed us to estimate the incidence and the prevalence of MS in St. Petersburg with the city population of just over 5 million. Patients (n=3150) with definite MS according to McDonald criteria 2010 were included in the study on March 1, 2017.

**Results:** The incidence rate in 2016y for St. Petersburg was 6,4/10<sup>5</sup> and prevalence rate was 60/10<sup>5</sup>. It's noted a gradual

increase in the incidence of the MS with 1-2/10<sup>5</sup> (2000-2007y) to 4,9/10<sup>5</sup> (2011y) and 6,4/10<sup>5</sup> (2016y). 70 % of patients with relapsing-onset MS and 50 % patients with progressive onset MS are women (sex ratio for RRMS m:f = 1:2,3). Types of MS distribution in our Center is 80% for RRMS, SPMS - 14% and PPMS - 6 %. The diagnosis was done at mean age of 34 with relapsing-onset MS and 45 with progressive-onset MS ( $p < 0,0001$ ). Men are diagnosed on average two years earlier than women ( $p < 0,0001$ ). Depending on the type of MS at the Center of observed patients with RRMS in younger age group (peak is 20-40 years,  $p < 0,0001$ ), older patients more often have progressive type (SPMS and PPMS,  $p > 0,08$ ) with peak of 40-60 years. 70 % of MS patients ( $n=2205$ ) receive DMD, among them 36% - glatiramer acetate, 50 % - interferones, 5% - natalizumab and others - fingolimod, mitoxantrone, cyclophosphamide, rituximab, azathioprine and in clinical trials.

The incidence of pediatric MS ( $< 18$  years) is 1,01/10<sup>5</sup> and the prevalence is 3,0/10<sup>5</sup>. About 10% patients had a first relapse in pediatric age, 2/3 of them was diagnosed of MS after 18 years. Only 2 patients with PPMS (less than 1 %) had onset before 18 years.

**Conclusion:** According to our study results St. Petersburg has high prevalence rate of MS. Increased incidence warrants further observation to clarify the truth of the growth and elimination of factors influencing a better detectability of MS and accessibility of health care.

## Disclosure

M Shumilina: nothing to disclose.

E Evdoshenko: support fees for board membership, consultancy or speaking, or grants, from Biogen Idec, Sanofi-Aven s, Genzyme, Pharmstandart, R-Pharm, Pharmsynte, Genfa Medica, Takeda and Generium.

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## EP1349

### Clinical and paraclinical characterization of Neuromyelitis Optica Spectrum Disorder in Venezuela: a multicenter study

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**Introduction:** Neuromyelitis Optica Spectrum Disorders (NMOSD) is an autoimmune demyelinating disease of Central Nervous System(CNS). Venezuela, according to recent publications shows the highest frequency cases of South America, however no previous characterization has been reported.

**Objectives:** To first characterize clinical and paraclinical NMOSD in Venezuela and create a data base.

**Methods:** In a descriptive, retrospective, multicenter study in a population with NMOSD from three centers: Centro Médico Docente La Trinidad, Hospital Universitario de Caracas, and Hospital IVSS Dr. Domingo Luciani. 104 clinical files were reviewed from April 2011 to April 2016. From the total of cases,

$n=86$  were selected based on complete data and inclusion criteria. Gender, age, age of onset, number of relapses, oligoclonal bands (OCB), AQP4-IgG status, Brain and Spine MRI, Visual Evoked Potentials(VEP) and Optic Coherent Tomography(OCT) were determined. Disability (EDSS), mobility (T25WT) were evaluated and cognitive profiles in a randomized subpopulation( $n=15$ ) were studied.

**Results:** Mean age was  $42.46 \pm 13.74$  and age of onset for NMOSD was  $33.13 \pm 14.69$ . Mean number of relapses  $5.22 \pm 4.74$ . Time from first to second relapse  $29.84 \pm 56.96$  months. (OCB) 15.41%. AQP4-IgG status positive 26%, negative 38%, unknown 36%. Coexisting autoimmune diseases 11.86%. EDSS  $4.39 \pm 2.26$ . T25WT  $9.23 \pm 4.65$ . First onset symptoms were LEMT 52%. Bilateral ON 26%, Unilateral ON 12%, Brainstem 10%.  $>3$  medullar segments in 52%. MRI brain lesions 35.71%. Bladder dysfunction 79.76%. Fatigue 75%, Painful Paroxistic Tonic Spams (PTS) 50.57%. Cognitive dysfunction was observed in 80% of a subpopulation showing severe cognitive impairment in working memory and processing speed domains.

**Conclusions:** Venezuelan population with NMOSD showed unique characteristics. A further analysis is required.

**Keywords:** Neuromyelitis Optica, characterization, multicenter, Venezuela.

## Disclosure

Nothing to disclosure.

## EP1350

### Demographic and clinical feature among patients with neuromyelitis optica in Iran

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**Background:** Neuromyelitis optica is a rare disease and epidemiological data on NMO is limited. The goal of this study was evaluation of demographic and clinical features of NMO in Caucasian population in Tehran, Iran.

**Method:** A cross sectional study among patients registered with NMO diagnosis was performed in Tehran during 2015 to 2016. We design a questionnaire to cover the epidemiological and clinical data of NMO in Tehran. Structured face to face interviews were conducted with 147 patients. The logistic regression was applied in analysis via software package SPSS.

**Result:** Among 147 patients, mean age was 36.09 years and 127 (86.4%) were female. Mean of disease onset age was 31.53 years. NMO-Ig G was positive in 71 (54.2%) patients and did not differ significantly between male and female (female positivity=56.3%, male positivity=42.1%;  $p$ -value=0.32). 42.2% of patients had primary presentation by transverse myelitis (TM) and optic neuritis (ON). In the next rank were patients presented only with TM (25.9%) or ON (18.4%). Totally 61 (46.6%) patients had a history of head trauma with 59 % NMO-Ig G positivity but it was not significantly higher than patients with no history of head trauma ( $p$ -value=0.38; OR= 1.44 (0.72-2.87)).

**Conclusions:** NMO is higher among female and younger age. Most of NMO patients present with TM and ON. Sex and history of head trauma did not significantly influence NMO-Ig G positivity.

### Disclosure

**Funding Source:** This study was funded by Tehran University of medical sciences.

**Conflict of Interest:** Authors declare no conflict of interest. The outcomes of this study examined some significant epidemiological factors and clinical features for NMO.

### EP1351

#### Care consumption of multiple sclerosis patients in France: an analysis of health insurance administrative databases using multichannel sequence analysis from 2007 to 2013

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**Background:** In France there is a lack of accurate and up-to-date data on care consumption of people with multiple sclerosis (PwMS). Identification of patterns among care pathways is helpful for understanding variation of practices and optimizing comprehensive care for PwMS.

**Objectives:** We aimed to describe care consumption of PwMS in France and identify specific patterns using multichannel sequence analysis (MCSA), an innovative method derived from social sciences.

**Methods:** A random sample from French health insurance databases was analysed for the period 2007-2013. As no clinical data was available, PwMS were identified in January 2007 thanks to a three-criterion algorithm using diagnoses of hospital admissions, disease-modifying therapies (DMTs) and multiple sclerosis (MS) long disease duration status. Care consumptions of interest were: consultations with general practitioners (GPs), private neurologists, private rehabilitation physicians, nurses, physiotherapists and hospitalizations for MS. These six dimensions were analysed simultaneously and led to classifying patients into homogeneous clusters.

**Results:** On the whole, 543 PwMS were identified with a median follow-up duration of 7 years. The sex-ratio was 2.8 with a median age of 48 years in 2007. MCSA revealed a 5-cluster typology of care consumption. A main group (n=271, 49.9%) corresponded to young patients with a probable recent MS onset, a remitting form and low disease activity. The 124 patients (22.8%) in the second group were more often treated in hospitals (received natalizumab) with a high number of visits to physiotherapists, probably reflecting an active disease. The third group (n=61, 11.2%) was routinely followed by private neurologists and almost all treated with a DMT (85.2%) possibly in relation with a controlled disease. The fourth group (n=47, 8.7%) included patients with high motor disability having a very high contact with physiotherapists, nurses and GPs, probably linked to a progressive phenotype. A defining feature of the last group of patients (n=40, 7.4%) was that they all deceased during follow-up. They were older, presented multiple comorbidities and had frequent contacts with nursing services.

**Conclusion:** This pioneer study, using an innovative method in health field, gives a first overview of patterns of care consumption of PwMS in France. Our results suggest that it is possible to identify from administrative databases groups of MS patients which are clinically relevant.

### Disclosure

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### EP1352

#### Prevalence and prognosis of multiple sclerosis in a cohort of Algerian patients

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**Introduction:** Multiple sclerosis (MS) is known to accumulate within families. It's a complexe neurological disorder resulting from an interaction between environmental and genetic risk factor. A lot of loci have been identified that playing a role in MS disease susceptibility. Although most MS cases occur sporadically, while this accumulation of cases clearly suggests that first-degree relatives of MS patients are at increased risk of MS, previous attempts to assess the magnitude of the familial MS risk have arrived at variable estimates.

**Aims:** To report the frequency of familial MS. To compare the demographic and clinical characteristics between those with and without a positive family history of MS. Evaluate the prognosis.

**Patients and methods:** All patients with MS are included in the study, the diagnosis is made according to the McDonald 2010 criteria. The family history of MS is obtained by the interview, demographic data including information on immediate family member and degree of relationship. Clinical information was sourced by neurological examination. The disability was appreciated by the EDSS.

**Results:** 450 MS patients were monitored at the Tlemcen University Hospital Neurology Department in 2017, 57 of them had a family history of MS. The prevalence of MS was 12.6%. They reported at least one first-degree relative. There was no significant demographic and clinical difference between FMS compared to the non-familial form. In 36% EDSS is greater than 6. 12% died 25-50 years. The familial form of MS is more severe, EDSS 6 is reached more rapidly than NSE.

**Conclusion:** The evolution is more severe in the familial form probably of the genetic context with the Maghrebian profile considered as severe.



## Disclosure

No conflict of interest

## MS and gender

### EP1353

#### Gender effect on cortical thickness measurements in primary progressive and relapsing remitting multiple sclerosis patients: a paired cross sectional study

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**Background:** Cortical demyelination and gray matter atrophy are more prominent to occur in primary progressive multiple sclerosis (PPMS) than in relapsing-remitting multiple sclerosis (RRMS) patients. PPMS course is more common in males while RRMS course is more common in females.

**Objectives:** To identify the differences regarding changes in cortical grey matter thickness (CGMT) between males and females PPMS patients as compared with RRMS patients.

**Methods:** Cross sectional, paired study comparing brain measurements of PPMS and RRMS patients using high resolution 3D brain MRI. Patients were matched by age, gender, and disease duration. Freesurfer 5.3 software was applied to obtain whole brain volumetric segmentation of subcortical regions and cortical thickness measurements. Paired t-test was performed to assess differences between groups.

**Results:** Ninety two patients were included, divided into 46 pairs of PPMS and RRMS patients; 25 female pairs mean±SD age 50±12yr, range 22-65yr, disease duration 10.7±8.5yr, and 21 male pairs age 50±10yr, range 31-67yr, disease duration 10.6±9.9yr. Cortical analysis of the female pairs demonstrated an overall decreased CGMT of the left hemisphere in PPMS as compared to RRMS patients (-11.67%, p=0.032), and no significant differences in the right hemisphere. Surface based analysis revealed focal clusters of decreased CGMT in the PPMS female group in the inferior-parietal and entorhinal in the left hemisphere and pre-cuneus, superior-frontal and pre-central gyri in the right hemispheres as compared to RRMS female patients (-11% to -15%, p<0.03). Cortical analysis of male patients demonstrated no significant difference between the groups.

**Conclusion:** Gender specific patterns of CGMT differ between female PPMS and RRMS patients.

## Disclosure

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Achiron Anat: Consulting fees: (EMD Serono, Genzyme, Roche); contracted research (Bayer, Biogen Idec, EMD Serono, Genzyme, Roche)

### EP1354

#### Brain MRI activity in multiple sclerosis (MS) before and after pregnancy

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**Introduction:** Postpartum disease and MRI activation is common among MS patients. In this study we tried to investigate the relation between Gd-enhancing lesions before and after pregnancy in Iranian MS patients.

**Patients and methods:** During a retrospective study between 2011 to 2016, we evaluated the medical records of all women patients with MS in our MS outpatient clinic in Shiraz Southern Iran. We detected that 75 patients had history of pregnancy in this period. These patients were selected. Demographic data, clinical findings, history of relapse, brain MRI findings and Gd-enhancing lesions during one year prior to pregnancy, type of medication, time of withdrawal of medications before pregnancy in one hand and history of relapse, MRI Gd-enhancing lesions, history of lactation during 9 months after pregnancy in the other hand were collected via a questionnaire. Statistical analysis was performed under supervision of statistical specialist.

**Results:** Seventy five MS patients were enrolled in the study. The mean age of the patients at the onset of pregnancy was 33.2±4.5 years. 76%, 86.7% and 70.7% of the patients were relapse-free in one year duration before, during and 9 months follow up after pregnancy. After pregnancy the rate of relapse increased significantly and 29.3% of patients had at least one relapse. (P value < .001) Presence of Gd-enhancing lesions in brain MRI during one year before pregnancy was significantly correlated with new Gd-enhancing lesions in brain MRI in 9 months follow up after pregnancy. (P value < 0.001)

Other factors such as type of medications and history of lactation did not have any significant correlation with MRI Gd-enhancing lesions or relapse after pregnancy.

**Conclusion:** Post-partum activation of the disease is common phenomenon among mothers with MS. In this study we showed that presence of Gd-enhancing lesions in MRI before pregnancy is correlated with MRI activity after delivery.

**Keywords:** Pregnancy, Multiple sclerosis, MRI, Gd-enhancing lesions

## Disclosure

There is no Conflict of interest.

### EP1355

#### Long term effect of delaying disease modifying therapy in patients with multiple sclerosis due to pregnancy planning

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**Background:** The effect of pregnancy on long-term disability in women with relapsing-remitting multiple sclerosis (MS) is poorly understood.

**Aim:** To determine the association between delaying Disease Modifying Therapy (DMT) for pregnancy planning and long-term disability, as measured by the expanded disability status scale (EDSS), in women with relapsing-remitting MS.

**Methods:** Using data from the Calgary MS Clinic database, we identified 426 women with EDSS < 5, who delayed starting DMT for more than one year after it was recommended during the period 1999 to 2006. Thirty-seven consenting women declined DMT due to planned pregnancy. EDSS at diagnosis was compared with EDSS at 5, 7, 10 and 15 years. The association between the cumulative time on DMT during the first 5 years of MS and EDSS change at 5, 7, 10, and 15 years was determined. EDSS change was compared with EDSS change in a control group of 101 women with relapsing-remitting MS (diagnosed between 18-40 years) who declined DMT for other reasons.

**Results:** Mean follow-up after diagnosis was 14.05 years. Prior to the diagnosis of MS 86.5% were nulliparous compared with 19% at the end of follow-up. Mean time to pregnancy was 2.38 years from MS diagnosis and 0.84 years from declining DMT for pregnancy. Eventually, 67.6% of the patients started DMT. Mean time to initiating DMT was 4.02 years after declining DMT for pregnancy. Confirmed relapses occurred in 70.3% of women between declining DMT due to pregnancy and starting DMT; the mean time to a relapse was 1.92 years. There was an increase in the mean EDSS score 15 years after diagnosis of 1.13 points (paired t-test,  $p = 0.002$ ) among women declined DMT for pregnancy planning. There was a moderate to high moderate negative correlation between the cumulative time on DMT during the first 5 years after the diagnosis of MS and EDSS change at 7 ( $R = -0.49$ ,  $p = 0.008$ ), 10 ( $R = -0.44$ ,  $p = 0.017$ ), and 15 ( $R = -0.67$ ,  $p = 0.006$ ) years. When compared to the control group who delayed DMT for other reasons, change in EDSS at 5, 7, 10, and 15 years was not significant even after adjustment for age.

**Conclusion:** Delaying DMT initiation for a planned pregnancy did not have a major impact of disability over 15 years in our patients despite the frequent occurrence of relapses and statistically significant change in EDSS. Greater time on DMT during the first 5 years after their MS diagnosis was associated with a statistically significant reduction in EDSS change.

## Disclosure

Seraj Makkawi: nothing to disclose.

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Luanne Metz has received grant support from Hoffmann La Roche.

## EP1356

### Differential gene expression in men and women with multiple sclerosis compared with healthy individuals

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**Background:** Multiple sclerosis (MS) is an autoimmune disease that affects women more than twice as often as men, a difference that is still increasing. Still, sex-related underlying differences in gene expression in MS patients and healthy controls (HCs) have only been scarcely investigated.

**Objective:** To analyze differentially expressed genes in women and men with untreated MS by comparing them with HCs of the same sex.

**Methods:** We included 30 women with relapsing-remitting (RR) MS and 28 HC women and 17 men with RRMS and 30 HC men. RNA was extracted from whole blood and gene expression levels measured by Affymetrix Gene 2.0 ST array. Data normalization and analyses were performed in Partek Genomics Suite and the enrichment of annotated genes was investigated using the database DAVID. We applied false discovery rate (FDR) ( $q < 0.01$ ,  $\pm 2$ -fold) on p-values to adjust for multiple comparisons.

**Results:** We found no differences between MS and healthy men and only PDK4 was higher expressed in MS women than in HC women (2.2-fold,  $q = 1.75 \times 10^{-9}$ ). Next we analyzed gene expression at  $\pm 1.3$ -fold difference by ANCOVA adjusted for age and scan-date ( $p < 0.05$ ) and observed 21 differentially expressed genes in women with MS and HCs, including a higher expression of HLA-DRB1, -DQA1, -DQB1, -DRA and -DRB5 in MS women. At the same conditions 158 genes were differentially expressed between men with MS and HCs, however only HLA-DRB1 and -DRB5 were significantly up-regulated in MS men compared to healthy individuals.

Functional annotation clustering, using the highest stringency, of all 21 genes identified 7 clusters of which 4 had significantly enriched ( $FDR < 0.01$ ) pathways and enrichment scores from 6.63 to 3.47. These 4 clusters consisted primarily of the above mentioned HLA-genes. In men functional annotation clustering of the 158 genes resulted in 8 clusters with the highest enrichment score of 2.13 encompassing genes from the type 1 interferon signaling pathway and a cluster with granzyme proteins, however these clusters were not significant after FDR correction.

**Conclusion:** Interestingly, of the HLA-genes only HLA-DRB1 and -DRB5 were higher expressed in both MS men and women. Most likely this reflects an effect of the MS-associated HLA-DRB1\*15:01 genotype. Of interest, the most differentially expressed gene in MS women (PDK4) is a mitochondrial protein involved in regulating the conversion of pyruvate to acetyl-CoA, and is inducible by several steroid hormones.

## Disclosure

Hannah-Marie Laigaard has nothing to disclose.

Annette Oturai has served on scientific advisory boards for Biogen and Genzyme; has received support for congress participation from Biogen, Novartis, Genzyme, and TEVA; has received speaker honoraria from, Biogen, Novartis, and TEVA.

Cecilie Ammitzbøl has received support for congress participation from Biogen, Merck, Genzyme, and TEVA.

Lars Börnsen has received support for congress participation from Biogen, Merck, Genzyme, and TEVA.

Per Soelberg Sørensen has received personal compensation for serving on advisory boards for Biogen, Merck, Novartis, Teva, MedDay Pharmaceuticals, and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck, Teva, GSK, and Novartis; has received speaker honoraria from Biogen, Merck, Teva, Sanofi-Aventis, Genzyme, and Novartis.

**Finn Sellebjerg** has served on scientific advisory boards for Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Teva, has been on the steering committee of a clinical trial sponsored by Merck Serono, and served as consultant for Biogen Idec and Novo Nordisk; has received support for congress participation from Biogen Idec, Novartis, Sanofi Aventis and Teva; has received speaker honoraria from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Schering-Plough.

**Helle Bach Søndergaard** has received support for congress participation from Biogen, Genzyme and Teva.

#### EP1357

##### **Fertility, maternal and pediatric development outcomes: interim report from the PREG-MS registry**

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**Background:** Multiple Sclerosis (MS) is commonly diagnosed in women of childbearing age and pregnancy management and outcomes are highly relevant to this patient population. PREG-MS, the first prospective regional MS pregnancy registry in the United States, follows women with MS and their children from pre-conception and any stage of conception to three years postpartum.

**Methods:** Detailed information on fertility, Assisted Reproductive Technologies (ART) disease modifying therapy (DMT) exposure, disease course, pregnancy course, and pediatric developmental outcomes is being collected through structured telephone interviews every 3 months, and medical records review.

**Results:** To date, study enrolled 50 women. 34% are in pregnancy planning stages, and 66% have either completed pregnancy or are currently pregnant with average time to conception of 3.4 (0.5-24) months. 30% of all subjects used ART. 10% of this group have failed one or more IVF cycles and all had moderate relapse within 6-months post treatment. Spontaneous 1<sup>st</sup> trimester pregnancy loss was 9%. 31% of pregnancies were exposed to DMTs including 2 patients who received glatiramer acetate (GA) throughout pregnancy. A third of patients reported pregnancy complications, regardless of DMT exposure, including preeclampsia, preterm labor, hypertension, low amniotic fluid, preterm amniotic sac rupture and excessive hemorrhage during labor. Preeclampsia and placental abruption were seen in mothers, and low birth weight and increased muscle tone at birth was seen in infant, with full-term GA exposure. Persistent motor developmental delay and ventricular septal defect were seen in infant of mother exposed to fingolimod. Infants born to non-DMT exposed mothers had low birth weights (22%) and reversible developmental delays (24%).

**Conclusion:** Data from this pregnancy registry contributes to our understanding of disease activity and DMT exposure effects on fertility, maternal and pediatric developmental outcomes. Prospective real world pregnancy registries can provide foundation for comprehensive disease management programs during pregnancy and postpartum.

#### **Disclosure**

Maria Houtchens: Unrestricted research grants from Biogen Idec, Genzyme Consulting honorarium from Teva Neurosciences, Biogen Idec, Novartis, Genzyme.

No conflicts with this abstract

Tatenda D Mahlanza: nothing to disclose

#### EP1358

##### **Inflammatory active peri- and postmenopausal patients in multiple sclerosis - a crosssectional study**

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**Objective:** The objective was to determine MS disease activity peri- and postmenopausal in comparison to not menopausal patients in our private practice in Hamburg, Germany. Disease activity was documented via MRI and relapse rate.

**Background:** MS is widely known as a common neurological disease in especially young female patients. But these patients get older, and data on disease activity in peri- and postmenopausal MS patients are scarce. According to lacking experience neurologists may expect, that after or around menopause MS disease activity may disappear and therefore stop disease modifying therapy.

**Design and methods:** In our private practice 410 women with MS were retrospectively enrolled into the study. Detailed information on the course of MS (relapses before 10, 5 and 2 years) as well as MRI-data in the most recent MRI (active T1-lesions, progress of T2-lesions) was obtained with a questionnaire developed for gynecologic and neurologic purposes.

**Results:** 304 questionnaires were included into analysis. 190 patients (62,5%) were not menopausal, 83 patients (27%) peri- and 24 patients (8%) postmenopausal, 7 patients (2%) remain unknown. As to expect relapse activity was higher in not menopausal patients (57%), but still 38% of the perimenopausal patients had relapses in the last 2 years.

Whereas 11,4% of the not menopausal patients had active T1-lesions, 7,1% of the perimenopausal patients showed activity in the MRI.

Progress in T2-lesions was higher in not menopausal patients (30,3%) compared to peri- and postmenopausal patients (14,1%).

**Conclusions:** Disease activity in MS seems to decline with older age and during hormonal changes (menopause) in female patients, but in some of the patients disease activity is persisting clinically and in neuroimaging even in a higher age.

Clinical and radiological disease activity should therefore continuously be monitored and disease modifying therapy adjusted accordingly.

#### **Disclosure**

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Birte Elias-Hamp: Has received speaker honoraria, payments for consultancy and research grants from Biogen, Merck Serono, Bayer Healthcare, Almirall, Novartis, Teva, Genzyme, Roche and received travel expense compensation from Bayer Healthcare, Biogen, Genzyme, Merck Serono, Novartis and Teva.

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Lena Feddersen: Has nothing to disclose.

Wolfgang-G. Elias: Has received speaker honoraria, payments for consultancy and travel expense compensation from Biogen, Merck Serono, Bayer Healthcare, Almirall, Novartis, Teva and Genzyme.

#### EP1359

##### **Pregnancy outcome and change in lymphocyte subset in peripheral blood in Japanese patients with multiple sclerosis after assisted reproductive treatment**

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**Background:** Multiple sclerosis (MS) predominantly affects females, with clinical onset during the childbearing years. In MS patients, assisted reproduction treatment (ART) may significantly increase the risk for a relapse. However, whether ART is related to relapse in Japanese patients with MS is unclear.

**Objective:** To determine the pregnancy outcome and whether Japanese patients with MS have an increased risk of relapse after ART.

**Subjects and methods:** We studied five Japanese patients in our hospital with relapsing-remitting MS (RRMS) who were treated with ART and five RRMS patients who became pregnant naturally. All patients received disease-modifying drugs. The relationship between ART and relapse occurrence was analyzed. Peripheral blood lymphocyte subsets were analyzed by flow cytometry. Pregnant patients treated with ART were compared to patients who became pregnant naturally. We studied the CD4+CXCR3/CD4+CCR4 ratio, CD8+CXCR3/CD8+CCR4 ratio, natural killer (NK) cells, and regulatory T cells before and during pregnancy, after delivery, and after failed ART.

**Results:** Four patients treated with ART became pregnant and delivered a baby, and one patient experienced a missed abortion. No patients used GnRH for ART. No relapses occurred in the year prior to ART, during pregnancy, or after delivery in patients with successful pregnancies. However, the RRMS patient who miscarried after IVF relapsed prior to ART and 2 months after the miscarriage. Peripheral blood lymphocyte subsets were not significantly different between patients treated with ART or not. The patient who failed IVF had increased NK cells at the time of abortion and a relapse compared with patients who became pregnant with/without ART.

**Conclusion:** No increase in relapses occurred in association with ART in patients with RRMS with stable disease activity. ART-related relapses may be associated with relapses in the year prior to ART and after failed IVF. Increased NK cells may be a cause of ART failure and relapse.

#### **Disclosure**

YS has received honoraria for talks from Bayer Yakuhin, and has received personal compensation for consulting services from Biogen Idec Japan, Teijin Pharma, Takeda Pharmaceutical Company and Novartis Pharma.

RI and KK have no conflicts of interest to declare. This work was supported by a Health and Labour Sciences Research Grant on Intractable Diseases (Evidence-based Early Diagnosis and Treatment Strategies for Neuroimmunological Diseases) from the Ministry of Health, Labour and Welfare of Japan.

#### EP1360

##### **Levels of serum anti-Muellerian hormone in women with relapsing-remitting multiple sclerosis**

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**Background:** Multiple sclerosis (MS) is a neurological disease mostly affecting women of childbearing age.

Recent studies suggest that MS may have a negative impact on fertility. In general, decreased ovarian reserve is supposed to be one of the most important factors for fertility impairment.

It is not known if ovarian decline contributes to accumulation of disability in women with MS when evaluated using the Expanded Disability Status Scale (EDSS). Anti-Mullerian hormone (AMH) is a peptide hormone that represents a simple and widely available measure of ovarian reserve unrelated to the menstrual cycle.

The purpose of this study was to determine AMH levels in females with relapsing-remitting MS (RRMS) in comparison with healthy volunteers.

**Methods:** A total of 104 reproductive-age females (mean age 33.3 ± 5.7) with RRMS and 107 age-matched healthy controls (HC, mean age 33.3 ± 5.6) were included in this case control study.

In females with MS, the median EDSS score was 2.5 points and the median disease duration was 5.1 years.

An enzymatically amplified two-site immunoassay was used to measure serum AMH level.

**Results:** On a group level, only an insignificant trend to reduced AMH values was found in RRMS patients (2.91±2.4 ng/ml) in comparison to healthy controls (3.50±2.6 ng/ml) (p = 0.09).

However, when being analyzed in 6 separated age-related subgroups, significant reduction of AMH values was found in MS patients at the age of 35-40 (2.2 ± 1.4 ng/ml) compared to age-related healthy controls (3.8 ± 2.1 ng/ml) (p=0.01).

AMH values were not associated with EDSS in MS patients, but showed significant decrease with age both in healthy controls and MS group.

**Conclusions:** In general, no clear reduction in follicular reserve was found in MS women comparing to healthy controls. However, when being analyzed in particular age-related subgroups, the AMH values were lower MS patients than in HCs at the age of 35-40. These results suggest possible negative impact of MS disease on fertility particular at the age above 35, which should be considered in parenthood planning.

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 Stourac: nothing to disclose.  
 Bednarik: nothing to disclose.

## MS symptoms

### EP1361

**Study on the adherence to the Spanish Neurological Society consensus guidelines on the treatment of multiple sclerosis generalized spasticity in Spanish multiple sclerosis units**  
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**Background:** The Spanish Neurological Society (SEN) 2013 consensus guidelines on the treatment of generalized multiple sclerosis (MS) spasticity recommend early control of spasticity triggers and other external factors and initiation of physiotherapy. At the stage where spasticity becomes troublesome and pharmacological treatment is required, the guidance reflects that the type of spasticity (generalized or focal/regional) determines two separate treatment pathways: while botulinum toxin is the option for focalized cases, baclofen or tizanidine are first-line treatments of choice for generalized spasticity. Diazepam is acknowledged also as an effective treatment for generalized spasticity but associated sedation advices to limit its use. In patients who respond inadequately to baclofen or tizanidine as monotherapy, second-line options are the use of THC+CBD oromucosal spray (Sativex) as add-on therapy or to use baclofen + tizanidine in combination; non-responders to each option can be switched over to the alternate option.

**Aim:** Dimension the adherence in Spanish multiple sclerosis units to the SEN 2013 consensus guidelines on the treatment of MS spasticity.

**Methods:** Retrospective, multicenter data collection of MS moderate to severe spasticity patients' features and treatments. Patients should have reached at least a second drug treatment at recruitment moment, and the data collected on MS and MS spasticity will go back in time as much as possible.

**Results:** 36 MS units were involved, data from 215 patients analyzed. Baseline data: mean age 52y, 62% women, mean 15y since MS diagnosis, mean EDSS score of 5.6, mean spasticity Ashworth scale score of 7.7(n=76), mean spasticity 0-10 NRS score of 2.7(n=52). Regarding their MS spasticity management, 48% had resourced to rehabilitation/physiotherapy and 2% to botulinum toxin. The first line generalized spasticity drug treatments reported were: 81% baclofen, 23% tizanidine, 16% benzodiazepines, 24% others. Second line treatments were: 7% baclofen + tizanidine, 94%, baclofen or tizanidine + THC:CBD spray.

**Conclusions:** The 2013 SEN MS spasticity management guidelines are heterogeneously followed across cases and centers. Reported use of rehabilitation/physiotherapy seems low, botulinum toxin use reflects a limited identification of partial spasticity,

baclofen is widely used as first line therapy, while use of THC:CBD as add-on is common in second line. Further educational activities on these guidelines seem required.

### Disclosure

Study sponsored by Almirall S.A.. No other conflicts of interest apply.

### EP1362

**Balance and gait impairment at the early stages of multiple sclerosis**

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**Background:** Impaired balance is one of the most important risk factors for falls in persons with multiple sclerosis (PwMS). Majority of the studies have been limited to PwMS with significant clinical disability. However, recent studies have suggested that even "PwMS with absence of clinical disability" (PwMS-AD) may also have balance and gait impairment. The aim was to evaluate balance and gait performance in PwMS-AD and compare them to "PwMS with minimal disability" (PwMS-MD) and healthy controls (HC).

**Methods:** 19 PwMS-AD with the Expanded Disability Status Scale (EDSS) score  $\leq 1.5$ , 16 PwMS-MD with EDSS  $\leq 3.0$  and 39 HC were assessed using a posturography, a laboratory-based movement analysis system and a clinical test, the Brief-Balance Evaluation Systems Test (Brief-BESTest). Limits of stability (LOS), postural stability (PS) and fall risk (FR) tests were performed. The Activities-Specific Balance Confidence Scale (ABC) was used to evaluate subjective confidence in balance. Walking ability assessed with Timed 25 Foot Walk Test (T25FW) and 12-Item Multiple Sclerosis Walking Scale (MSWS-12).

**Results:** Both MS groups had significantly worse LOS, PS and FR scores according to HC. Significant differences were found between PwMS-AD and healthy controls in all domains of LOS, PS and FR tests ( $p < 0.05$ ), with an exception of the difference in anteroposterior PS ( $p > 0.05$ ). There was a significant difference in Brief-BESTest and T25FW scores ( $p < 0.05$ ) but no significant difference was found in the ABC scale score ( $p > 0.05$ ) between PwMS-AD and HC. In addition, significant differences were observed between PwMS-AD and PwMS-MD in terms of PS, Brief-BESTest, T25FW, MSWS-12, ABC ( $p < 0.05$ ).

**Conclusion:** This study has suggested that the PwMS-AD have impaired balance and gait performance compared to HC; however, subjective confidence in balance is not significantly different from HC. Although walking speed and balance parameters were affected before disability occurs in MS subjects, when minimal disability occurs, anteroposterior PS and subjective confidence in balance become significantly different according to the HC. Although the PwMS-AD do not complain about the balance and gait impairment, they should be assessed regularly regarding to

balance with clinical and laboratory-based analysis tools. This can lead to early detection of impaired balance and fall risk to design appropriate rehabilitation programs.

### Disclosure

All authors declare nothing to disclose

### EP1363

#### Presence of occipital neuralgia predicts high cervical spinal cord lesion in multiple sclerosis

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**Background and purpose:** Neuropathic pain can be the presenting feature or occur during relapses of Multiple Sclerosis (MS). The association of trigeminal neuralgia with MS has been well documented and is typically related to a pontine lesion. Limited data exists regarding occipital neuralgia in patients with MS. We tested the hypothesis that occipital neuralgia in MS is associated with high cervical spinal cord lesions (C2-3).

**Methods:** We reviewed the records of 29 patients diagnosed with both occipital neuralgia and MS, clinically isolated syndrome or radiologically isolated syndrome (RIS) by a neurologist at our institution from January 2001 to December 2014. We collected data on demographics, disease course of MS, description of pain, sensory findings, comorbid headache disorders, history of trauma, presence of C2-3 demyelinating lesions, and treatment response.

**Results:** The patients with both occipital neuralgia and MS were typically female (76%) and had a later onset (age > 40) of occipital neuralgia (72%). Of those (28 patients) with available imaging for review, 18 patients (64%) had the presence of a C2-3 lesion. The majority of patients with a C2-3 lesion had unilateral symptoms (83%) and episodic pain (78%). All patients with documented sensory loss (3/3) had a C2-3 lesion. Six out of the 8 patients with progressive MS (PMS) (75%) had a C2-3 lesion with the remaining 2 patients having a potential alternative cause to their occipital distribution headache with moderate to severe cervical spondylotic changes on imaging. Of the 8 patients with a C2-3 lesion and imaging at onset of occipital neuralgia, 5 (62.5%) had evidence of active demyelination with enhancement on MRI. All of the 8 patients with long term follow-up that had either relapsing remitting MS (5/5), RIS (2/2) or transverse myelitis (1/1) had a good response (as defined by pain freedom for greater than 1 month) after treatment with occipital nerve blocks (ONB) and/or high dose intravenous (IV) steroids. None of the patients with PMS (3/3) responded to treatment with ONB or high dose IV steroids.

**Conclusions:** Predictors of an association between occipital neuralgia and presence of a C2-3 lesion were unilateral episodic symptoms, sensory loss, onset occurring later in life (age > 40), and PMS phenotype. Patients with PMS did not respond to ONB or high dose IV steroids, whereas other phenotypes responded to those treatments.

### Disclosure

Narayan R. Kissoon: nothing to disclose  
James C. Watson: nothing to disclose  
Orhun H. Kantarci: nothing to disclose

### EP1364

#### Cognition is not cognition: different aspects of cognitive deficits in MS patients

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During the past years, increasing attention is being paid to operationalize cognitive deficits in MS-patients. Thereby it is generally assumed that affected persons suffer from cognitive decline in the course of the disease. Cognition itself is not a singular ability of the brain but indeed consists of various skills.

**Objective:** The aim of the study was to evaluate, whether the disease affects cognition in general or whether various aspects of cognitive dysfunction are impaired in particular.

**Methods:** 123 MS patients have been examined by the The Vienna Test Expert System Traffic, a test system which has been established for testing driving ability skills. It consists of 5 different parts, each one tests an aspect of cognition: reaction time (RT), reactive stress tolerance (DT), visual orientation performance (LVT), attention, concentration (COG), observational ability and skills in gaining an overview (ATAVT). We examined by t-Test if there were any significant differences between the test outcomes. Furthermore, we analyzed if there were any connections between disease duration and cognitive deficits.

**Results:** The mean age of the 123 patients was 41,2 years ( $SD = 10,7$ ), 21% were male and 79% female. Mean EDSS was 1,5 ( $SD = 1,6$ ) and mean disease duration 123,4 months ( $SD = 102,7$ ). The t-Test revealed that the patients had better test results in the test measuring attention and concentration compared with the other tests. There was a significant difference between attention/concentration and reaction time ( $t(22) = 7.172, p < .001$ ), visual orientation performance ( $t(244) = 5.705, p < .001$ ), observational ability ( $t(237.2) = 3.768, p < .001$ ) and reactive stress tolerance ( $t(241) = 5.302, p < .001$ ). There was also a significant correlation between disease duration and all kinds of cognitive deficits: disease duration and RT ( $r = -.22, p < .05$ ), ATAVT ( $r = -.21, p < .05$ ), LVT ( $r = -.26, p < .01$ ), DT ( $r = -.29, p < .01$ ) and COG ( $r = -.41, p < .01$ )

**Conclusion:** In comparison to a normal population, cognitive deficits of the examined MS patients include reaction time, visual orientation performance, observational ability, reactive stress tolerance and skills gaining an overview. In contrast, attention and concentration are not affected. Cognition is not impaired as a whole but in single aspects. Furthermore, disease duration was linked to cognitive decline.

### Disclosure

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### EP1365

#### Prognostic assessment of cognitive impairment, fatigue development and depression according to brain lesions in patients with multiple sclerosis

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**Background:** Multiple sclerosis (MS) is a chronic, progressive, inflammatory, autoimmune, neurodegenerative disease of central



nervous system. Prevalence of cognitive impairment in patients with multiple sclerosis (MS) ranges from 40 to 70%. Presence of cognitive dysfunction at the early stages of the disease is an unfavourable prognostic factor for the disease progression.

**Objectives:** Prognostic assessment of cognitive impairment, fatigue development and depression according to demyelinating lesions in patients with multiple sclerosis.

**Methods:** Cognitive impairment assessment was conducted using Montreal cognitive assessment scale (MoCA). For detecting fatigue was used Krupp's Fatigue Severity Scale (FSS). Depression was detected using Beck's Depression Inventory (BDI). For prognostic assessment of cognitive disorders, fatigue or depression development in case of presence of lesions in the white matter of the brain (with various localization or characteristics), we determined the relative risk of their detection depending on presence or absence of demyelinating process in a particular area of the brain (risk assessment in terms of odds ratios - OR and 95% CI).

**Results:** A total of 170 patients have been examined: 57 - with cognitive decline, 62 - with symptoms of fatigue, 51 - with depression. In case of atrophy of the corpus callosum, statistically significant increased risk of cognitive impairment in MS patients was determined (OR = 26 (3,40-198,9),  $p = 0.0001$ ). Prognostic assessment of fatigue symptoms reliably depended on the presence of the atrophy of corpus callosum (OR = 2,82 (0,98-8,11),  $p = 0.047$ ), lesions in the parietal lobes (OR = 2,46 (1,02- 5.9),  $p = 0.041$ ) and confluent lesions (OR = 2,58 (0,96-6,97),  $p = 0.05$ ). Statistically significant prognostic assessment of depression development in MS patients was obtained by the following indices: the corpus callosum atrophy (OR = 2,81 (1,15-6,86),  $p = 0.021$ ), lesions in the temporal lobes (OR = 5,22 (2,29-11,89),  $p = 0.001$ ) and confluent lesions (OR = 3,45 (1,42-8,41),  $p = 0.005$ ).

**Conclusions:** particular localization of demyelinating lesions in the white matter of the brain may be a prognostic factor for the development of cognitive and emotional disorders in patients with multiple sclerosis.

## Disclosure

Nothing to disclose

## EP1366

### Cognitive dysfunction in a Spanish cohort with multiple sclerosis: evaluation of cognitive reserve and other predictive factors

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Cognitive dysfunction(CD) in multiple sclerosis(MS) is one of the most disabling symptoms of the disease, affecting 30-65% of patients. Most commonly affected cognitive domains are memory, attention and processing speed. The protective effect of cognitive reserve(CR) has been demonstrated. We aim to analyze the prevalence of CD and the type of domain impairment in a Spanish MS cohort. In addition, we examine the effect of CR, mood disorders, fatigue, psychiatric drugs, demographic and clinical variables on cognitive performance(CP).

We enrolled MS patients over 24 years old diagnosed according to the McDonald Criteria 2011. We excluded patients with other neurologic diseases or conditions that may affect CP(relapses,

corticoid treatment or changes in disease modifying therapies in the last 4 weeks, psychiatric disorder...). We used Rao abbreviated Neuropsychological battery to analyse the prevalence of CD; educational level, years of education, professional complexity, vocabulary knowledge and leisure activities to evaluate CR; and validated questionnaires for demographic variables, clinical forms of MS, EDSS, fatigue, anxiety and depression.

We included 62 MS patients(74.2% women) with a mean age of 39.98 years. The prevalence of cognitive dysfunction was 38.7%. Verbal memory (64.5%) and processing speed(32.2%) were the most affected domains. Educational level( $p=0.014$ ), years of education( $p=0.004$ ), professional complexity( $p=0.005$ ), vocabulary knowledge( $p=0.006$ ), and leisure activities( $p=0.014$ ) were associated with a better CP in univariate analyses. Disability( $p=0.045$ ) and the usage of psychiatric drugs( $p=0.002$ ) were associated with worse CP in univariate analyses. Multivariate logistical regression model showed that low scores in leisure activities( $p=0.031$ ) and vocabulary knowledge ( $p=0.047$ ) were independent variables for prediction of CD in MS.

Our results confirm a similar prevalence of CD and the type of domain impairment in a Spanish MS cohort as previously described in the literature. We also confirm a protective value of CR(measured by leisure activities and vocabulary knowledge) in the appearance of CD in MS.

## Disclosure

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Prieto León M: nothing to disclose

Casado Chocán JL: nothing to disclose

Uclés Sánchez AJ: nothing to disclose

## EP1367

### Validation and cross-cultural adaptation of the Composite Autonomic Symptom Score-31 (COMPASS-31) in Croatian and Serbian multiple sclerosis patients

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**Aim:** To validate and cross-culturally adapt both Croatian and Serbian versions of the Composite Autonomic Symptom Scale-31 (COMPASS-31) questionnaire for the detection of dysautonomia in multiple sclerosis (MS).

**Methods:** A total of 179 patients, 67 with clinically isolated syndrome (CIS) and 112 with MS at two MS centers (Zagreb and Belgrade) between April 1 and October 31, 2016 completed the COMPASS-31 questionnaire. Demographic and clinical data, including age, gender, MS phenotypes and the Expanded Disability

Status Scale (EDSS) were collected. Internal consistency of the Serbian and Croatian versions of the COMPASS-31 was evaluated using Cronbach's alpha coefficient. Test-retest reliability of scores was evaluated by calculation of the intra-class correlation coefficient (ICC). Receiver operating characteristic (ROC) curve analysis was used to determine a cut-off value of COMPASS-31 total score.

**Results:** The Cronbach's alpha coefficient of total COMPASS-31 for the Croatian MS sample was 0.844 and for the Serbian MS sample 0.779. Joint analysis demonstrated range of Cronbach's alpha coefficients from 0.394 to 0.796, with values of four domains higher than 0.700. In both Croatian and Serbian samples, and in the total group, the Cronbach's alpha coefficient of COMPASS-31 was 0.785. Reproducibility measured by ICC was acceptable (0.795). With regard to the clinical validity, significant correlation ( $p < 0.001$ ) was found between EDSS and the total COMPASS-31 score. Furthermore, significant differences between MS phenotypes were detected for Bladder and Gastrointestinal domains, and for the total COMPASS-31 score ( $p < 0.001$ ,  $p = 0.005$ , and  $p = 0.027$ , respectively). Finally, significant differences between MS phenotypes in the proportion of participants with score  $> 0$ , implicating the existence of at least one of the symptoms investigated in each domain, were detected for Secretomotor and Bladder domains ( $p = 0.015$  and  $p < 0.001$ , respectively). According to the ROC analysis, the highest sensitivity and specificity was detected for Orthostatic intolerance domain. The COMPASS-31 questionnaire sensitivity was 94.4% for MS patients who were experiencing orthostatic intolerance symptoms prior to testing; the specificity was 82.4%.

**Conclusions:** COMPASS-31 represents a valid and well accepted, self-assessment instrument for detection of dysautonomia in MS.

## Disclosure

Jelena Drulovic serves on scientific advisory boards for Bayer Schering Pharma, Merck Serono, Teva, Genzyme, a Sanofi Company, and received honoraria for speaking from Merck Serono, Teva, Bayer Schering, Genzyme, a Sanofi Company, Medis, Roche; and has also received research grant support from the Ministry of Education and Science, Republic of Serbia (project no. 175031).

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## EP1368

### Are inhibitory and excitatory neurotransmitter levels in the posterior cingulate cortex associated with MS fatigue?

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**Background and aims:** Fatigue is one of the most debilitating symptoms for MS patients. However, the role of neurotransmitters such as Gamma aminobutyric acid (GABA) and Glutamate in the pathology of fatigue is poorly understood. In this study, we utilized two-dimensional localised correlation spectroscopy (2D L-COSY) to determine if there was any association between GABA and Glutamate+Glutamine (Glx), in the posterior cingulate cortex, with clinical fatigue in relapsing remitting MS (RRMS).

**Methods:** 58 adult RRMS patients and 44 age and sex matched healthy subjects (HC) were recruited to the study. All patients were undergoing treatment with Fingolimod or Interferon or Glatiramer Acetate therapy. Self-reported fatigue status was measured on all participants using the Modified Fatigue Impact Scale (MFIS). All participants were scanned on a Siemens Prisma 3T MR system with 64 channel head coil and 2D L-COSY was acquired from a 3x3x3 cm<sup>3</sup> voxel in the normal appearing posterior cingulate cortex (PCC) with TE<sub>initial</sub>=30ms and 96 increments. Spectral analysis was undertaken using Felix software with all peaks normalised to total creatine (tCr) as an internal reference. To evaluate the differences in fatigue status between MS and control groups, independent student t-tests were used. Correlation (Spearman's rho) assessed the association between fatigue scores with GABA and Glx levels.

**Results:** Total MFIS, physical fatigue and cognitive fatigue were significantly increased by 54.35%, 59.6% and 49.12%, respectively, in RRMS compared to HCs ( $p \leq 0.05$ ). The levels of PCC GABA/tCr and Glx/tCr in RRMS were significantly reduced by 3.22% and 4.52% ( $p \leq 0.05$ ), respectively, compared to those in HCs. In RRMS, we saw a positive association between GABA and Glx ( $r = 0.28$ ,  $p \leq 0.05$ ). However, there was no significant correlation between either Glx/tCr or GABA/tCr PCC levels with fatigue levels in RRMS.

**Conclusions:** The reduced levels of GABA and Glx in this study may reflect pathological alterations in RRMS patients with fatigue. The close link between GABA and Glx, primarily glutamate, production in the GABAergic pathway could explain the

positive association. Although we could not find a correlation with fatigue levels, this study is the first to investigate changes in these neurotransmitters using 2D L-COSY in MS fatigued subjects.

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### EP1369

#### Correlation of fatigue with cognitive and physical disability using clinical outcomes and MRI measurements

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**Introduction:** Fatigue is an underestimated symptom affecting up to 95% of patients with multiple sclerosis (MS). It doesn't only exacerbate impairment, but also affects a patient's sense of control over the illness. In order to help patients cope with this disabling but treatable aspect of MS, it is necessary to understand the correlation between fatigue domains, cognitive functioning, and physical ability.

**Methods:** Adult MS patients diagnosed as relapsing remitting (RRMS) or progressive were clinically evaluated. The Modified Fatigue Impact Scale (MFIS) was administered to both MS and healthy age-and-sex-matched control subjects. Processing speed was assessed using the Symbol Digit Modality Test (SDMT) and global brain atrophy was evaluated using MRI examinations. 3DT1 and 3DFLAIR images were acquired and processed. Intracranial volume (ICV) and subcortical gray matter structures, lateral ventricles and corpus callosum were segmented and their volumes measured using the volBrain pipeline (<http://volbrain.upv.es>) and the SIENAX tool in FSL. Univariate analysis was performed to explore differences between subjects with and without fatigue. Multivariate analysis controlling for age, gender, education level, EDSS, disease duration, clinical depression, and MS type and treatment was performed to see the correlations between fatigue and the different variables.

**Results:** 113 MS patients with mean disease duration of 8.6 years and 57 healthy subjects were recruited. Significant fatigue was seen in 32.3% of MS patients and 6.2% in controls. Among fatigued MS participants, 66% and 75% had respective physical and cognitive fatigue. Multivariate analysis showed that SDMT correlated negatively with fatigue ( $p=0.001$ ,  $OR=0.88$ ), more specifically with its cognitive domain ( $p=0.003$ ,  $OR=0.9$ ). In addition, Physical fatigue positively correlated with EDSS ( $p=0.04$ ,  $OR=1.4$ ), particularly with the pyramidal FS score ( $p=0.031$ ,

$OR=2.5$ ). In multivariable linear regression and adjusting for age, disease duration, EDSS, and depression, there was a negative correlation between MFIS scores and ICV ( $\beta = -0.54$ ,  $p < 0.0001$ ) and a positive correlation with the volume of lateral ventricles ( $\beta = 0.37$ ,  $p=0.006$ ) and all-ventricular volume ( $\beta = 0.35$ ,  $p=0.007$ ).

**Conclusion:** There is an association between cognitive fatigue and SDMT, as well as physical fatigue with EDSS pyramidal FS score. There is also an association between cognitive and physical fatigue and brain atrophy.

### Disclosure

All authors have no conflict of interest to disclose.

### EP1370

#### Sleep disorders in patients with multiple sclerosis and their link with fatigue

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**Introduction:** Recent studies propose that patients with Multiple Sclerosis (MS) are at increased risk for sleep disturbances and they are undiagnosed. Fatigue is perceived as one of the most disabling symptoms in MS. The relation between fatigue and sleep disturbances is a subject of study due to it is not yet fully understood.

The primary endpoint of this study is to analyze the prevalence of sleep disorders in a cohort of adult patients with MS evaluating the link between these disorders and their clinical features (type of MS, disease duration, clinical severity, presence of spinal demyelinating lesions and presence or absence of Interferon).

The other main objective is to evaluate the relations between sleep disturbances and fatigue of the MS patients enrolled in the study.

**Methods:** Fifty-nine patients with MS took part in this cross-sectional study. Participants completed standardized validated questionnaires related fatigue (Modified Fatigue Impact Scale-MFIS) and sleep disturbances (Insomnia Severity Index-ISI, STOP-BANG questionnaire, Pittsburgh Sleep Quality Index -PSQI and patients who meet International Restless Legs Syndrome Study Group criteria for the diagnosis of Restless Legs Syndrome completed Restless Legs Syndrome Rating Scale-RLS).

**Results:** As concerns sleep evaluation, 35.6% patients suggesting RLS, 54.2% have insomnia (ISI score >5), 10.2% have a high or medium risk of Sleep Apnea Syndrome (SAS) according to the STOP-BANG questionnaire and 35.6% patients were considered fatigued (MFIS >45).

Statistical analysis showed that clinical findings are not associated with sleep quality and sleep disturbances; except high risk of OSAS which was associated with disease duration (U-test=77.500;  $p=0.041$ ).

Patients with fatigue show higher prevalence of poor sleep quality ( $p=0.012$ ) and sleepiness ( $p=0.001$ ) with higher PSQI scores (U-test=225.000;  $p=0.006$ ) and sleepiness score (U-test=201.000;  $p=0.001$ ). They have higher prevalence of RLS ( $p=0.022$ ), insomnia ( $p=0.000$ ), and OSAS ( $p=0.018$ ), with higher severity of symptom: U-test=235.500,  $p=0.002$ ; U-test=170.500,  $p=0.000$  and U-test=245.500,  $p=0.009$  respectively.

**Conclusions:** The present study demonstrates the association between MS and a higher prevalence of sleep disorders. Besides,



it shows the close link between insomnia, sleepiness, sleep quality, OSAS presence, RLS and fatigue. On the contrary, sleep quality and sleep disorder are not related with the analyzed clinical findings.

### Disclosure

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### EP1371

#### Patient-reported outcomes are worse for progressive-onset MS than relapse-onset MS, particularly early in the disease process

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**Background:** Dramatic progress has been made for people with relapse-onset multiple sclerosis (MS). However, for the 15% progressive-onset MS cases, the knowledge is limited, and only ocrelizumab was recently confirmed as an effective therapy. To increase our knowledge and improve disease management for progressive-onset MS, understanding the differences between the two MS onset types is vital.

**Objective:** To examine differences between progressive-onset MS and relapse-onset MS in relation to disability, disability progression, MS symptoms and quality of life on the basis of patient-reported outcomes.

**Method:** The Australian Multiple Sclerosis Longitudinal Study (AMSLS) database of 1985 cases was used in this cross-sectional study. Associations between onset-type and outcomes were assessed with negative binomial regression and adjusted for confounders such as age, disease duration, gender, and age of diagnosis.

**Results:** Seventeen of the nineteen outcomes of progressive-onset MS patients were significantly more severe than relapse-onset MS patients after adjustment for confounders, including disability, progression over the last year, fatigue, sensory symptoms, walking difficulties, pain, balance, sexual dysfunction, bladder problems, bowel problems, spasticity, anxiety, depression and EQ-5D (the adjusted mean ratios ranged from 1.11 to 1.52). Importantly, the difference between the two onset types was most pronounced early in the disease process and reduced with increasing MS duration, with the interaction between onset types and MS duration being significant for disability, progression over the last year, walking difficulties, bladder problems, bowel problems and spasticity.

**Conclusions:** People with progressive-onset MS were significantly worse off on nearly all patient-reported outcomes compared to relapse-onset MS counterparts. The differences were most pronounced early in the disease course. The findings support the work of the International Progressive MS Alliance and highlight the urgency of identifying early interventions for progressive-onset MS.

### Disclosure

Yan Zhang: nothing to disclose  
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### EP1372

#### Perceived cognitive impairment and cognitive test performance assessment in multiple sclerosis patients

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**Background:** Discrepancy might exist between perception of cognitive functioning and cognitive performance in multiple sclerosis (MS) patients, as a consequence of under- or overestimation of cognitive dysfunction.

**Objective:** The aim of this study was to explore the correlation between perceived cognitive dysfunction on a self-reported questionnaire and performance on specific cognitive domains and Brief Repeatable Battery (BRB) in a cohort of patients with MS.

**Methods:** Between November 2015 and December 2016, 94 relapsing-remitting MS patients afferent to our MS center were asked to complete the Perceived Cognitive Deficit (PCD) questionnaire, an 11 item self-reported assessment tool exploring the patient perceived degree of cognitive impairment in 6 major cognitive domains (verbal memory, visuo-spatial memory, learning, sustained attention and concentration, speed of information processing, and verbal fluency). Answers reported on a 5-degree scale were further converted into dummy variables (yes/no) according to low (grade 1-3) or high (grade 4-5) self-perception of cognitive impairment. Domain-specific perceived cognitive performance was then correlated with corresponding scores in selective BRB subtests exploring verbal memory (SRT-LTS, SRT-CLRT), visuo-spatial memory (SPART), learning (SRT-D SPART-D), sustained attention and concentration (SDMT), speed of information processing (PASAT-3, PASAT-2) and verbal fluency (WLG).

**Results:** Out of 94 included patients, 29 were men and 65 women. Mean age was 44.3±8.5 years. Mean duration of the disease was 10.7±5.2 years. Mean schooling values were 14.1±3.5 years. 35 patients perceived a deficit of verbal memory while a deficit was found in 44. 25 patients perceived a deficit of visuo-spatial learning while a deficit was found in 38. 26 patients perceived a deficit of learning while deficit was found in 52. 33 patients perceived a deficit of sustained attention and concentration while a deficit was found in 49. 26 patients perceived a deficit of speed of information processing while a deficit was found in 59. 28 patients perceived a deficit of verbal fluency while a deficit was found in 19.

**Conclusions:** Results of our study showed a discrepancy between perceived and estimated cognitive impairment. For most of the cognitive domains patients underrated cognitive dysfunctions while the perception of deficit of verbal fluency was overestimated.

### Disclosure

None

### EP1373

#### Continuous facial myokymia and hemifacial spasm at initial presentation of multiple sclerosis

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**Introduction:** Involuntary facial movements including continuous facial myokymia (CFM) and hemifacial spasm (HFS) are rare clinical manifestations of multiple Sclerosis (MS). CFM is characterised by rhythmic, vermiform movement of unilateral facial musculature with MS being the most common aetiology. Meanwhile, HFS presents with irregular, synchronous unilateral tonic or clonic facial muscle contractions which is very rarely associated with MS. We present three patients with abnormal facial movements at initial neurology review who were subsequently diagnosed with MS.

**Case 1:** 37-year-old man presenting after two months of diverse focal neurological symptoms. Left sided CFM noted on examination. MRI showed florid T2 lesions in brain, brainstem (left mid-brain/pons) and spinal cord with multiple contrast enhancing lesions.

**Case 2:** 46-year-old woman presenting with right sided CFM. She had a previous episode of transient right leg numbness. MRI showed multiple T2 lesions in the brain and spinal cord but none involving the brainstem (previously presented at the Association of British Neurologists conference 2017).

**Case 3:** 47-year-old man presented with HFS recorded by patient on video which spontaneously resolved. MRI showed one subcortical and two periventricular T2 lesions but no brainstem lesion. He declined investigation at this point. Six years later he developed an ataxic gait and MRI showed progression.

All patients fulfilled the 2010 Revised McDonald Criteria for a diagnosis of MS.

**Discussion:** There are only 2 case reports of CFM and 1 case report of HFS as the presenting symptom of MS in the literature. CFM is usually associated with an ipsilateral lateral pontine lesion on MRI. Only one of the two patients demonstrated this lesion. HFS is commonly attributed to a vascular compression of the facial nerve. However, in MS, an ipsilateral facial nucleus lesion has occasionally been described although not in our case. Although MS presenting with HFS or CFM is rare, knowledge of the association is essential to enable timely diagnosis. These cases also demonstrate that typical MRI lesions may be absent.

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Oliver Cousins: Nothing to disclose

S Harikrishnan: Nothing to disclose

Yoshua Collins-Sawaragi: Nothing to disclose

## EP1374

### Symptoms of bowel dysfunction in people with multiple sclerosis

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**Background:** Overall prevalence of bowel dysfunction symptoms is unknown in people with multiple sclerosis (PwMS). This is due to variations in definition and reticence of patients and clinicians to discuss them. Faecal incontinence is recognised as life

changing whilst constipation is often dismissed as minor, but our findings report otherwise.

**Methods:** 237 PwMS were assessed for eligibility of a randomised controlled trial at 12 centres throughout the United Kingdom. Symptoms were recorded at the initial assessment visit whilst ano-rectal dysfunction tests were undertaken at one centre.

**Results:** 29 (12.2%) did not meet the inclusion criteria i.e. troublesome constipation, with a further 17 (7.1%) meeting the criteria, but were not randomised. 35 males and 154 females were recruited with a mean age of 52.3 years (SD 10.83), duration of MS 14.3 years (SD 9.18). 106(56.1%) reported having relapsing remitting MS, 59(31.2%) secondary progressive and 22 (11.6%) primary progressive, with 88 (46.6%) using unilateral or bilateral assistance to walk 20-100m. 71(37.6%) reported they had had constipation for more than 10 years, 82(44.4%) from 2-10 years and 34(28%) less than 2 years. 150(79.4%) reported severity of symptoms as moderate or severe. The primary symptom was bloating 162(85.7%), straining more than 50% of the time 123(59.3%), incomplete emptying more than 50% of the time 151(79.8%) and spending from 5 to 20 minutes per attempt at evacuation was found in 111 (59.1%) participants. Analysis of the ano-rectal sub-study indicated that 15(65.2%) had slow transit. 112 (59.3%) participants were passing stool 2-4 times per week.

**Discussion:** Constipation is not just infrequent passing of stool. Considerable time, effort and discomfort is associated and such questions need to be asked when assessing bowel dysfunction. Our qualitative data supported our quantitative findings in that often PwMS required significant time for toileting and were reluctant to leave home without going to the toilet or indeed use public toilets. Furthermore, bloating is embarrassing with some females being mistaken for being pregnant; incomplete evacuation is very uncomfortable, whilst overflow incontinence may not be recognised as a diagnostic symptom that may require hospitalisation.

**Conclusion:** Symptoms of constipation are multifactorial and awareness of the impact on quality of life needs to be raised so that effective and timely management can be implemented.

## Disclosure

None

## EP1375

### The role of fatigue and cognitive impairment in early retirement due to multiple sclerosis

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Multiple sclerosis (MS) is the most common cause of non-traumatic neurological disability affecting mainly young adults during their best working years. For the past couple of decades fatigue as well as neuropsychological deficits have been recognized to be crucial symptoms in majority of the patients. It seems that majority of the patients are unable to retain employment long term and retire soon after the diagnosis is made. We have previously reported the median time for the disability pension to be 6 years. Therefore, we aimed to evaluate the role of cognitive impairment

and fatigue in the risk of early retirement due to MS in a community dwelling MS cohort.

Patients diagnosed with MS between 2000 and 2016 were collected from the electronic patient records. The retention rate of retirement was evaluated by Kaplan Maier method. The presence of fatigue was collected from the patient files and the presence of cognitive impairment from the neuropsychological assessments. Both results were analysed by the Cox proportional hazard regression analysis.

Altogether 260 patients were identified (63 males and 197 females). 56/260(21.5%) patients were retired by the time of the analysis and 66/260(25.3%) patients had gone through a neuropsychological assessment. 115/260(44.2%) patients suffered from fatigue and 59/260(22.7%) patients from other neuropsychological symptoms. Fatigue was a risk factor for the retirement (age adjusted HR 2.78 (95% CI 1.59-4.34)) but the presence of cognitive dysfunction or deficit in any of the domains in neuropsychological testing showed no statistical significance (age adjusted HR 1.22 (95% CI 0.73-2.1)).

Fatigue in patients with MS is a major risk factors for early retirement. There is a clear unmet need to find effective therapies for fatigue to prevent early retirement. We did not find the presence of neuropsychological deficits to be an independent risk factor for early retirement due to MS. This might be due to the previously found correlation to the EDSS and disease duration.

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## EP1376

### Symptoms related to multiple sclerosis: experience based on the systematic data collection from an electronic device

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**Objective:** The appropriate measurement and management of symptoms related to multiple sclerosis (SymR-MS) could improve the quality of life of patients. Clinician-rated measures of these symptoms purport to be objective but do not measure the patient's experience and may not be sensitive to changes that are meaningful to the patient. In addition, obtaining this crucial information is often time-consuming and therefore not routinely collected. We present our experience in the systematic data collection of a total of 10 validated scales for different SymR-MS from an electronic device. The patients complete the scales in the waiting room and the data are automatically uploaded to the electronic medical records being evaluated in real time by the neurologist.

**Material and methods:** The analysis included MS clinical form, Disease Modifying Therapies (DMT), administration route and a total of 10 patient-based measures including Numeric Rating

Scale (NRS) for Spasticity, Penn Spasms Frequency Scale, Bladder Control Scale, Sleep Quality Scale, Gait Quality Scale, NRS for pain, Barthel index, Fatigue Severity Scale, The European Quality of Life-5 dimensions and Sexual Satisfaction Scale.

**Results:** 20 patients with MS (80% RRMS, 20% SPMS) and 13 controls were analyzed. Most of patients (75%) were treated with first line DMT (44% oral, 33% subcutaneous). Patients with MS had a higher Kurtzke scale (EDSS) ( $p > 0.001$ ), increased spasticity ( $p = 0.006$ ) and greater gait difficulty ( $p = 0.007$ ) than controls. Patients with SPMS complained of greater spasticity ( $p = 0.001$ ), frequency of spasms ( $p = 0.002$ ), gait difficulty ( $p < 0.001$ ), degree of dependence ( $p = 0.027$ ), worse bladder control ( $p = 0.028$ ) and worse sexual satisfaction ( $p = 0.034$ ) than controls. When comparing SPMS and RRMS patients, these differences were significant only for gait difficulty ( $p = 0.027$ ). Patients with EDSS  $> 3.0$  complained of worse spasticity ( $p = 0.007$ ), bladder control ( $p = 0.009$ ) and gait difficulty ( $p = 0.002$ ) compared to patients with EDSS  $< 3.0$ . No significant differences were observed with respect to DMT or route of administration. In the correlation analysis, the parameters related to a worse quality of life were the sleep disorders and the pain.

**Conclusions:** The application of an electronic method in the collection of SymR-MS provides crucial information in real time during the visit of the patient. In our experience allows us to systematically quantify these symptoms and make appropriate therapeutic decisions.

## Disclosure

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Merchán Ruiz, Miguel reports no disclosures.

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## EP1377

### Analysis of pre-randomization run-in data demonstrates muscle cramps and spasms are common, and associated with pain in MS

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**Background:** FLX-787 is a TRPA1/TRPV1 ion channel activator that is efficacious in decreasing muscle cramp intensity in an electrically-induced cramp (EIC) model in healthy volunteers, and cramp frequency in otherwise healthy subjects with nocturnal leg cramps (NLC). Muscle cramps result from spontaneous activity arising from hyperexcitability of  $\alpha$ -motor neurons in the spinal cord. FLX-787 is believed to dampen  $\alpha$ -motor neuron hyperexcitability by chemical -rather than electrical- neurostimulation. In this process, TRPA1/TRPV1 activation in the oropharynx and esophagus leads to excitatory sensory input to stimulate brainstem nuclei and subsequently descending spinal tracts to inhibit motor neuron hyperexcitability. The Flex-201 study was initiated in patients to evaluate the safety and efficacy of FLX-787 in a disease state where cramps, spasms and spasticity are prevalent, such as Multiple Sclerosis (MS).



**Objectives:** To monitor the prevalence of cramps/spasms and pain severity in MS subjects during a 14-day placebo run-in period. Cramp/spasm frequency and subject-reported spasticity and pain were analyzed. The analysis was performed to confirm that the baseline signal was adequate, and initial power assumptions were appropriate.

**Methods:** Flex-201 is a multicenter, randomized, blinded, cross-over study to investigate the effects of FLX-787 in subjects with MS and symptoms of spasticity, spasms and cramps (n up to 60). Interactive voice response system (IVRS) data from the run-in period were analyzed to quantify cramps/spasm frequency, spasticity and pain. Pearson correlation analysis was performed to identify statistical associations between these datasets.

**Results:** This analysis of partial (n=25) run-in data demonstrated that 80% of subjects experienced  $\geq 9$  cramps/spasms, and 40% of subjects experienced  $\geq 25$  cramps/spasms over the 14-day run-in period. Pain was a common complaint reported by 84% of subjects. Muscle cramp/spasm frequency was highly correlated with self-reported pain ( $p=0.0002$ ), and stiffness to a lesser degree ( $p<0.05$ ).

**Conclusion:** Correlations from this analysis suggest that subjects who experience higher cramp/spasm frequency suffer more pain. Given the potential of FLX-787 to reduce both muscle cramp frequency and pain, seen in healthy subjects with nocturnal leg cramps, if FLX-787 can reduce cramp/spasm frequency and alleviate pain, then the selected study population should allow these effects to be measured in subjects with MS.

## Disclosure

1. Glenn Short is an employee of Flex Pharma and Flex Pharma Stock Holder.
2. Brooke Hegarty is an employee of Flex Pharma and Flex Pharma Stock Holder.
3. Jennifer Szegda is an employee of Flex Pharma and Flex Pharma Stock Holder.
4. William McVicar is an employee of Flex Pharma and Flex Pharma Stock Holder.
5. Christoph Westphal is an employee of Flex Pharma and Flex Pharma Stock Holder.
6. Thomas Wessel is an employee of Flex Pharma and Flex Pharma Stock Holder.

## EP1378

### Cognitive dysfunction and pseudobulbar affect comorbidity in MS

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**Background:** Pseudobulbar affect (PBA) is a neuropsychiatric syndrome where an individual's affect does not reflect their mood. It is characterized by periods of involuntary laughing or crying that may occur without any distinct stimulus. PBA episodes are typically exaggerated and do not match how the person feels. It commonly occurs in people with neurological conditions or injuries like stroke, amyotrophic lateral sclerosis, traumatic brain injury, Alzheimer's disease, Parkinson's disease and multiple

sclerosis (MS). PBA has been reported in approximately 10% of MS individuals. Cognitive dysfunction (CD) is estimated to affect about 60% of MS patients and may occur at early or late stages of the disease. Common CD changes in MS include decreased memory, information processing, attention, executive function, visuospatial function and verbal fluency. Impairments in cognitive function have been postulated to be more common in MS patients with PBA than those without PBA.

**Purpose:** To examine the frequency at which MS individuals with clinically proven CD also have PBA. The secondary objective was to examine the relationship of specific cognitive components in people with PBA.

**Method:** MS subjects with self-reported CD underwent computerized cognitive testing (NeuroTrax Mindstreams (NTM)) and completed questionnaires regarding PBA (Center for Neurologic Study-Lability Scale), and Beck Depression Scale, Fatigue Severity Scale and QOL (SF-36).

**Results:** Of a total of 32 participants, 24 (75%) had CD as measured by NTM of which 11 (46%) had PBA. Of those with self-reported CD that did not have demonstrable deficits by NTM, only 1 (12.5%) had PBA. Although of no statistical significance, patients with PBA scored lower than average on memory and motor skills. Scores on executive function, attention and information speed were better than memory and motor skills. No significance was found for relationship between CD and depression or fatigue ( $P > .05$ ). The only QOL component that significantly correlated with CD was physical function ( $P < .05$ ).

**Conclusion:** We documented a high incidence of PBA in MS individuals with demonstrable CD, at a rate that far exceeds the reports of PBA in the overall MS population. CD in individuals with PBA was not driven by any specific domain and followed a similar pattern of those without PBA. Studies to evaluate these relationships at a greater scale are warranted and might reveal common pathophysiologic mechanisms.

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Cecilie Fjeldstad, PhD has nothing to disclose.

## EP1379

### Early life residence in Gulf is associated with rapid multiple sclerosis progression in young Egyptians

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**Background:** There is increasing evidence that environmental factors play a role in the development and may be progression of multiple sclerosis (MS).

**Objectives:** To assess MS severity and progression in MS Egyptian patients who have been residing in Gulf area in their early life.

**Patients and methods:** The study design was retrospective case-control approved by the Review Board of Neurology Department, Cairo University. The medical records of 21 patients with relapsing remitting MS (RRMS) in a tertiary referral center in Cairo were reviewed. Those patients were residing

in Gulf in their early life (15 patients were born in Gulf and stayed till adolescence and 6 started living there since their early childhood and settled for at least 10 years) (group 1). The clinical and radiological parameters of these patients were compared with age and gender matched 21 RRMS patients who lived their entire life in Egypt (group 2).

**Results:** There were no significant differences between the two groups regarding age of disease onset, time from onset to diagnosis, or from diagnosis to treatment. The most frequent presenting symptom was motor dysfunction in group 1 (38.09%); and optic neuritis (ON) in group 2 (33.33%). The median Expanded Disability Status Scale (EDSS) was significantly higher in group 1 than in group 2 (5 vs. 3.5;  $P$  0.03). Median durations from disease onset to EDSS of 4 and 6 were significantly shorter in group 1 compared with group 2 (3 and 6.5 years vs. 5.5 and 8 years;  $P$  0.02 and 0.001 respectively). Number of infra-tentorial lesions was higher in group 1 ( $P$  0.04); otherwise no differences in the number of black holes, supratentorial lesion load or contrast enhancement on initial MRI brain between both groups.

**Conclusions:** More rapid progression of MS course is observed among Egyptian RRMS patients who had their early life in Gulf, which points to a possible role of environmental factors characteristic of Gulf region in disease severity and progression.

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#### EP1380

##### Clinic model for intrathecal baclofen therapy in patients with multiple sclerosis: a retrospective review

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**Background and Purpose:** Limited research has been conducted evaluating the benefits of Intrathecal Baclofen Therapy (ITBT) in Multiple Sclerosis (MS) patients, specifically ambulatory patients. This study demonstrates a possible ITBT patient care model for patients with MS in the clinical setting.

**Methods:** Post Hoc chart reviews completed at MS Center at Oklahoma Medical Research Foundation (OMRF), Oklahoma City, Oklahoma, USA, a multidisciplinary MS clinic offering ITBT for previous 6 years. Review included standard MS care, ITBT screening, referral and monitoring process, continued ITBT management and functional outcome measures. Demographics, disease status and clinical outcomes were compared with overall MS population.

**Results:** Clinic model of ITBT treatment sequence: Identification by provider; Physical Therapy (PT) evaluation; ITBT trial with PT monitoring; decision of patient with providers for surgical referral and surgical pump implantation; ongoing management of ITBT dose, rehabilitation, and MS care.

Demographics Data (n=54):

Patient gender ratios; percentages of Relapsing Remitting MS, Primary Progressive MS, Secondary Progressive MS, and Neuromyelitis Optica mirrored general MS population.

Clinical Care Data:

Average time since diagnosis: 17 years  $\pm$ 15; Average time ITBT 42.3 months  $\pm$ 38; gait speeds stable over 24 months of ITBT; no preference indication of Disease Modifying Therapies; 54% required additional oral antispasmodics or onabotulinumtoxin A injections; average daily dose of baclofen was 470.29mcg/day.

**Discussion:** An integrated referral model can be used to identify and effectively treat MS patients with spasticity. OMRF patients mirrored demographics of general MS population. Ambulatory patients' function remained stable over 24 months. Average daily dose and use of additional antispasmodics are also consistent with literature. ITBT in MS clinics using this model can be used to treat spasticity as comprehensive symptom management. Further research regarding decision algorithms and functional outcomes need to be addressed.

**Conclusion:** Management of ITBT in MS patients includes similar demographics to the MS population. This ITBT model may be used as guide for clinics to implement ITBT. Additional antispasmodic may be required for optimal spasticity management in MS patients.

#### Disclosure

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Tania Reyna, MD: nothing to disclose.

#### EP1381

##### Cognition, depression and clinical disease activity in the course of MS: a 4 year follow up

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Cognitive deficits in MS-patients have moved into the focus of interest in the past few years. Many studies have demonstrated that the disease leads to cognitive decline. Cognition itself is not a singular ability of the brain but indeed consists of various skills.

In a follow-up study we examined different cognitive abilities in MS-patients using the Vienna Test Expert System Traffic which has been established for testing driving ability skills.

**Objective:** The aim of the study was to look for the change of different aspects of cognition after a 3-4 year follow-up and their association with depression, disease activity and physical impairment.

**Methods:** 40 patients with relapsing remitting MS at baseline and a 3-4 year follow-up have been examined by using cognitive tests (MUSIC), a fatigue scale (FSMC), two depression scales (HAMD, BDI II) and the Expert System Traffic of the Vienna Test System consisting of 5 subtests including reaction time, reactive stress tolerance, visual orientation performance, attention, concentration, observational ability and skills in gaining an overview. The mean value-differences between the examinations were compared by Mann-Whitney-U-Test.

**Results:** Between baseline and follow-up 41% of patients suffered from one or more relapses. During this time 43% changed their prophylactic medication. The medium EDSS score increased

from 1.54 to 1.57. There were no significant differences between the results in the Vienna Test System. Depression ( $M_{\text{Baseline}} = 11.55$ ,  $M_{\text{FollowUp}} = 11.15$ ) fatigue ( $M_{\text{Baseline}} = 60.50$ ,  $M_{\text{FollowUp}} = 59.26$ ) and cognitive impairment ( $M_{\text{Baseline}} = 22.28$ ,  $M_{\text{FollowUp}} = 23.5$ ) didn't show any significant differences either. The asymptotic significance of all variables ranged between  $p = .337$  and  $p = .996$ . More than 40% of the MS-patients showed disease activity in terms of relapses, which led to a change of prophylactic medication. The results of all kinds of cognitive testings remained stable in all aspects within 4 years.

**Conclusion:** Despite the fact that the disease was clinically active in almost half of all patients, there was no significant change in cognitive performance or in depression. Disease activity does not necessarily lead to cognitive decline.

### Disclosure

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### EP1382

#### The spectrum of acute cardiopulmonary events associated with multiple sclerosis exacerbations

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**Introduction:** Acute neurological injuries may cause acute cardiopulmonary (CP) events including neurogenic pulmonary oedema (NPO) and Takotsubo cardiomyopathy (TTC). Sympathetic overstimulation is an important mechanism underlying central nervous system (CNS) deleterious effects on pulmonary and cardiac function. Focal CNS lesions, including demyelinating lesions in multiple sclerosis (MS), may cause CP disturbances.

**Objective:** Describe acute CP events associated with acute MS relapses.

**Methods:** We present the case of a 32 year-old woman with TTC after a brainstem MS exacerbation. We review the literature on acute CP events, specifically NPO and TTC, associated with MS relapses.

**Results:** A 32 year-old woman with a 3-year history of relapsing MS treated with subcutaneous interferon beta-1a presented with a brainstem exacerbation and active MS lesions in the cerebellum, cerebral peduncles, pons, right frontal and left occipital lobes on brain magnetic resonance imaging (MRI). After a 3-day course of intravenous (IV) methylprednisolone her deficits improved partially. Three weeks later, she presented with lethargy and chest tightness. Her electrocardiogram showed inverted T waves and she had elevated serum troponin levels. Echocardiography showed basal left ventricular (LV) akinesia consistent with TTC. Brain MRI revealed a new enhancing lesion in the left medulla. She completed a 3-day course of IV methylprednisolone with improvement of her symptoms and resolution of LV dysfunction.

Our literature review identified 30 relapsing MS patients with acute CP events in the setting of MS exacerbations. They presented with NPO (n=8), TTC (n=12), or concurrent unclassified myocardial dysfunction and pulmonary oedema (n=10). 26 patients had acute demyelinating lesions in the brainstem. In 21 cases, these lesions involved the medulla. 24 patients received treatment with high dose IV steroids. Three patients died but most survivors had a favourable outcome after treatment.

**Discussion:** NPO and TTC are increasingly recognized complications associated with acute brainstem MS relapses. Active demyelinating lesions involving the medulla may damage vasomotor centers at the dorsomedial medulla leading to autonomic dysfunction with profound sympathetic overstimulation. Clinicians should be aware that new cardiac or pulmonary symptoms may accompany MS relapses that involve the brainstem; the risk of CP complications of such attacks requires further systematic study.

### Disclosure

Cristina Valencia-Sanchez: nothing to disclose

Dean M. Wingerchuk: nothing to disclose

### EP1383

#### Multiple sclerosis and cognition: the impact of psychotropic medications

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**Background:** Psychotropic medications can potentially impact cognitive performance. MS consequences can impact mood, but MS can also directly impact both cognition and/or mood. Regardless of whether mood is a consequence of disease or disability, psychotropic medications are frequently prescribed. Limited data objectifies the degree/pattern that psychotropic medications impact cognitive performance in people with Multiple Sclerosis (PwMS).

**Aim:** To explore the association between the chronic use of psychotropic medications and cognitive function in PwMS.

**Methods:** PwMS completed a standardized validated computerized cognitive assessment battery (NeuroTrax) with analysis of age- and education-adjusted individual cognitive domain scores and a global cognitive (average) summary score (GCS). Use of chronic psychotropic medications were uniformly recorded and PwMS were requested not to take these within 6 hours prior to testing. Depression was evaluated (Beck Depression Inventory). Analysis of covariance determined the effect of each psychotropic medication on cognitive scores, while controlling for the impact of other medications, depression, cardiovascular risk factors, thyroid disorder and EDSS.

**Results:** 699 PwMS were evaluated [Female: 526 (75%), EDSS 2.7±2, Education years: 14.5±2.7]. Antidepressants, benzodiazepines, stimulants (modafinil, methylphenidate, amphetamine-salts, amantadine), anticonvulsants, spasmolytics, opioids, fampridine, anticholinergics and 5HT-antagonists were used by 296 (42%), 141 (20%), 94 (13%), 94 (13%), 91 (13%), 70 (10%), 22 (3%), 20 (3%), and 16 (2%) patients, respectively. Use of anticonvulsants, anticholinergics and 5HT antagonists was independently associated with decreased global cognitive scores, but



effect sizes were miniscule [ $P=0.005$ ,  $0.02$  and  $< 0.001$ , partial  $\eta^2=0.01$ ,  $0.01$  and  $0.02$ , respectively). The number of impaired cognitive domains ( $>1SD$  below age-education average) was slightly, but significantly higher with these medications. Other medications (including antidepressants, stimulants) had no significant impact on objective cognitive scores.

**Conclusion:** As long as chronic psychotropic medications are not taken in the 6 hours prior to testing, they do not substantially interfere with NeuroTrax cognitive assessments of PwMS.

### Disclosure

Glen M. Doniger is an employee of NeuroTrax corporation. All other authors have nothing to disclose.

### EP1384

#### The comparison of core stability and trunk position sense in patients with multiple sclerosis and healthy controls

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**Introduction:** Motor and sensorial problems are seen at various grades due to influence of central nervous system in patients with Multiple Sclerosis (MS). Motor and sensory parameters such as core stability and body position sense must be at sufficient level for a good balance and postural control.

**Purpose:** To compare core stability and trunk position sense in mild to moderately disabled MS patients according to healthy individuals.

**Method:** 45 MS patients (EDSS, median=2 (1-3)) and 29 healthy individuals of similar age and sex were included in the study. Core stability was examined with assessing core endurance and core power. Core endurance was assessed with trunk flexion test, modified Biering-Sorensen test, prone bridge test, right and left lateral bridge tests; core power was assessed with sit-ups and modified push-ups tests. Trunk position sense was assessed using J-Tech Dualer IQ digital inclinometer with trunk reposition tests. Measurements were made at 2 levels; Lumbosacral (LS) and Thoracosacral (TS) regions. Tests were performed on eyes open-firm surface, eyes closed-firm surface and eyes open-foam surface.

Comparison of core stability and trunk position sense were assessed with Mann Whitney U and Wilcoxon tests.

**Results:** As a result of the study, it was seen that all parameters of core endurance, core power and trunk position senses of MS patients were decreased statistically significantly according to the control group ( $p < 0.05$ ).

**Conclusion:** These results indicate that core stability and trunk position sense decreased in patients with MS according to healthy individuals. Although the level of disability is low, from the early stage of disease, we think that investigating the core stability and the trunk position sense and planning the necessary intervention is important to improve postural control and balance.

### Disclosure

There is no conflict of interest and source of funding.

### EP1386

#### Emotional status in relapsing remitting MS patients

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Multiple Sclerosis (MS) is a chronic inflammatory, demyelinating and degenerative disease of Central Nervous System. The aim of the present study was to evaluate depression, anxiety and alexithymia, which are often associated with MS. 98 subjects were recruited: 51 patients affected by Relapsing Remitting (RR) MS (18 males and 33 females) and 47 healthy controls (CG) (18 males and 29 females) matched by gender, age and education. We recruited participants aged between 23 and 60 (SM group Age:  $\bar{x} 45 \pm 9.89$ ; Education  $\bar{x} 13 \pm 3.58$ ; Expanded Disability Status Scale (EDSS)  $\bar{x} 2.8 \pm 2.05$ ; CG group Age:  $\bar{x} 46 \pm 10.72$ ; Education  $\bar{x} 14 \pm 2.63$ ). Diagnosis and type of MS and EDSS score were established by a neurologist not involved in the study. All patients underwent a clinical evaluation, including Beck Depression Inventory (BDI-II), The State-Trait Anxiety Inventory (STAI-Y) for state (STAI y1) and trait (STAI y2) anxiety, the Toronto Alexithymia Scale (TAS) and the Frontal Assessment Battery (FAB). None of the subjects obtained a pathological score in the clinical evaluation. We performed a one way ANOVA and a Bonferroni correction was used to analyze the differences between MS patients and CG. The differences were considered significant at  $\alpha=0.0125$ . MS group obtained higher and statistically significant scores at BDI-II ( $p=0.005$ ), TAS ( $p=0.002$ ), and at STAI-Y, both as regards the trait anxiety, STAI-y1, ( $p=0.0001$ ) and as regards status anxiety, STAI-y2, ( $p=0.00009$ ). A correlation study also showed a positive correlation (0,30) between the EDSS scores and alexithymia predisposition. The MS scores at TAS were not pathological, but an higher score at the EDSS correlated with an higher score at TAS. In addition, a negative correlation occurred between FAB and BDI-II (-0,38). An higher score at the BDI-II corresponded to a lower score at FAB and viceversa. Within the MS group, all the clinical scales correlated to each others. In our study MS patients do not have a full-blown depression or anxiety or alexithymia. Our results seem to suggest that our MS patients, although not achieving pathological scores, still have a lower mood and an heightened anxiety compared to CG. These results seems to indicate the importance of an accurate evaluation of the psychological status of the MS patients.

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### EP1387

#### Effects of anxiety on motor imagery abilities in persons with multiple sclerosis

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**Background:** Motor imagery is defined as the ability to mentally perform movement without movement execution. Although motor imagery has been used in many populations for a long time, its importance as a possible therapeutic tool for persons with multiple sclerosis (pwMS) has been recently understood. In order to add motor imagery into the rehabilitation programs, it is necessary to examine possible situations that may affect it. Since motor imagery processes play a crucial role in the experience of anxiety, it is also important to know the effects of anxiety on motor imagery abilities. Although there is relatively little evidence about how motor imagery is affected by anxiety in healthy people, to the best of our knowledge, this situation has been never examined in pwMS. The aim was to compare motor imagery abilities in pwMS with and without anxiety.

**Methods:** This cross-sectional study enrolled 27 pwMS. The participants were divided into two groups according to the cut off  $\geq 8$  on the Hospital Anxiety and Depression Rating Scale-A. Motor imagery ability was assessed using the Kinesthetic and Visual Imagery Questionnaire (KVIQ) and mental chronometry test for the Timed Up and Go (TUG) test. Temporal congruence between actual and imagined TUG was expressed as delta time calculated according to the formula: (actual TUG - imagined TUG)/[(actual TUG + imagined TUG)/2] x 100.

**Results:** There were 12 participants with anxiety and 15 without anxiety. Although the clarity of the image (KVIQ-Visual) and intensity of the sensations (KVIQ-Kinesthetic) were not significantly different between the groups ( $p > 0.05$ ), the participants with anxiety had less clarity of the image and intensity of the sensations with medium and small effect sizes (Cohen's  $d = -0.62$  and  $-0.39$ , respectively). No significant difference was observed in the delta time of TUG tests ( $p > 0.05$ ); however, the effect size was medium (Cohen's  $d = -0.51$ ).

**Conclusions:** Although the significance levels were not enough, the effect sizes have suggested that the pwMS with anxiety have less clarity of the image and intensity of the sensations, and temporal congruence between actual and imagined movements. These findings suggest that motor imagery ability can be affected by anxiety in pwMS and further studies with larger sample size were highly warranted.

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## EP1388

### Evaluation of sleep quality and risk assessment of obstructive sleep apnea among MS patients

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**Background:** Multiple sclerosis is a demyelinating disease, marked by deficient neural conduction and axonal loss. Fatigue as a common complaint of MS patients has several possible explanations. Sleep disorder contributes to chronic fatigue and decreased sleep quality is reported among MS patients. We aimed to assess the sleep quality and risk of obstructive sleep apnea (OSA) among MS patients and see whether severity of MS is correlated to sleep quality.

**Method:** 514 MS patients including 70 men and 435 women were enrolled in the study. Age range was 13 to 67. Basic demographic and disease characteristic data was collected from all patients. Disease severity was assessed by extended disability score scale (EDSS). Sleep quality and sleepiness was assessed by Pittsburgh sleep quality index (PSQI) and Epworth sleepiness score (ESS). Likelihood of OSA was assessed using the Berlin and STOP-BANG questionnaires.

**Results:** Regarding the quality of sleep, the mean  $\pm$  SD of PSQI score was  $6.6 \pm 3.2$  with 60.9% of the patients having poor sleep quality. ESS results however showed that 8.6% of the patients reported mild to severe sleepiness during the day. In regards to likelihood of OSA, evaluation of patients with STOP-BANG questionnaire revealed that 13 percent of the patients had high risk for OSA; Berlin questionnaire also indicated that 21.2 percent of the patients had high likelihood of sleep disordered breathing. PSQI scores were weakly correlated to the patients' EDSS score (P value: 0.02,  $r = 0.4$ ). Berlin questionnaire results were also correlated to the patients' EDSS score (P value: 0.04,  $r = 0.35$ ).

**Conclusion:** Our results indicates that MS patients have poor sleep quality and that OSA could be partially relevant. We also found that MS severity directly affects sleep quality.

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## EP1389

### Preliminary fatigue subtype discovery from the MS mosaic study

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**Background and Goals:** Greater than 80% of MS patients experience significant fatigue during their clinical course. Several assessment tools attempt to characterise fatigue, but they have significant limitations and are too infrequently administered to represent this highly dynamic symptom. As a result, intervention studies poorly assess response, and MS patients undergo commonly ineffective empiric treatment trials. Progress in our understanding and management of MS fatigue requires more frequent symptom reporting, nearly continuous data collection on effect modifiers, and effective analytic tools capable of interpreting multiple data types. To improve our understanding of fatigue among people with MS, we developed a novel mobile application that

captures data on many of these variables and utilises novel machine learning methods to identify patterns within this data to improve our understanding of fatigue.

**Methods:** MS Mosaic is a longitudinal study (NCT02845635) that combines data from a mobile platform with existing biomarkers and then utilises machine learning methods to help reveal a more comprehensive picture of MS. Initial focus on data analysis has been on improving fatigue characterisation. Continuously collected data from participants' daily symptom surveys, medication diaries, weekly study tasks (timed walk, PASAT, finger tapping, 9-Hole Peg Test), and mobile sensors (sleep, steps) is analysed through a Bayesian generative hierarchical model that uses a Dirichlet process at a higher level and then represents the observed data at a lower level, providing a particular patient's "fatigue group" memberships.

**Results and Conclusions:** Fatigue subtypes can be discovered using MS Mosaic app data, and machine learning clustering methodology. Clustering analysis from the MS Mosaic Study provides readily identifiable subtypes (with the use of monitoring platforms like MS Mosaic) and will prove useful in the design of upcoming fatigue intervention studies.

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### EP1390

#### Epilepsy in multiple sclerosis (MS): clinical, electroencephalographic (EEG) and magnetic resonance imaging (MRI) characteristics

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**Introduction:** In according to classical viewpoint epilepsy in MS is thought to be neither frequent, nor typical clinical manifestation. Precise mechanisms of epileptic seizures in MS patients and their relation to disease are still poor understood.

**Aims:** to investigate clinical phenotype of epileptic seizures in MS and to evaluate their relations to MS characteristics, EEG and MRI abnormalities.

**Patients and methods:** Among 1850 patients from local MS registry of Tatarstan Republic epileptic seizures were noted in 48. All patients with epileptic seizures besides clinical neurological evaluation undergo routine EEG (NeuroSoft) and MRI (Siemens, 3T; besides routine, double inversion recovery (DIR) sequences was performed for better cortical lesions visualization).

**Main results:** The prevalence of epilepsy among patients with MS in Tatarstan Republic was 2,59% (48/1850). The most frequent seizure types were partial (33%) and secondary generalized (71%). In most (90%) cases epileptic focus was clinically located in frontal or temporal lobes. Among rare variants 1 case of Kojevnikovs epilepsy, and 2 cases of epileptic cortical myoclonus were noted. In all cases epilepsy was associated with relapsing remitting (52%) or secondary progressive (48%) MS. Notably, epilepsy was also associated with more rapid MS progression: median MS severity scale (MSSS) score was 5,88 vs. 5,24 in total MS population. In 19% of cases seizures occurred before

diagnosis MS, in 29% they were associated with MS relapses, in 52% such association was not observed. Regional and generalized epileptiform discharges on EEG were noted in 48 and 10% respectively. Correlation of seizure pattern, epileptiform discharges and lesions on MRI was noted in 27% cases, but with DIR sequence such correlation became higher - up to 50%. Antiepileptic therapy was completely successful in only 73% of cases.

**Conclusions:** Typically epilepsy in MS is presented with partial and secondary generalized seizures from frontal and temporal lobes, and associated with poor prognosis and unsatisfied treatment response.

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### EP1391

#### Patient-based outcome measures of the impact of disease in patients with multiple sclerosis and vitamin D deficiency

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**Introduction:** Vitamin D deficiency is currently regarded as a potential environmental risk factor for multiple sclerosis (MS) but the clear relationship between low vitamin D levels and disease manifestations and severity is not certainly established.

**Aim:** We performed a cross-sectional study aimed to investigate the relationship between vitamin D status, depression and self-reported impact of disease in patients with MS.

**Methods:** 106 patients treated with immunomodulatory drugs in the MS center of our hospital were included. Depression was assessed with the Beck Depression Inventory for Primary Care and patient-reported impact of MS was assessed with the Multiple Sclerosis Impact Scale (MSIS-29v2). Serum 25-hydroxyvitamin D levels were measured by *chemiluminescence* immunoassay method and 30 nanograms/milliliter was considered the cut-off point for deficiency.

**Results:** Mean age of the patients was 38.7+/- 10.1 years, with a female/male ratio of 2.1/1. Median EDSS score was 2 points (25-75 IQR 1.5-2.5). Mean serum 25-hydroxyvitamin D level was 23.2 +/- 11.8 nanograms/milliliter and 86 patients (81.1%) had low vitamin D levels. Median MSIS-29v2 - PHYS scores were 21 points (25-75 IQR 20.5-27) in patients with normal vitamin D levels and 32 points (25-75 IQR 24-48) in patients with vitamin D deficiency (p=0.0002). Median MSIS-29v2 - PSYCH scores were 13.5 points (25-75 IQR 10-17.5) in patients with normal vitamin D levels and 18 points (25-75 IQR 13-24) in patients with vitamin D deficiency (p=0.009). Depression was diagnosed in 10% of the patients with normal vitamin D levels and 19.7% of the ones with vitamin D deficiency (p=0.5).

**Conclusions:** We found no significant association between low vitamin D levels and depression but the physical and psychological patient-based outcome measures of the impact of multiple



sclerosis were significantly worse in patients with vitamin D deficiency.

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## Clinical assessment tools

### EP1393

#### Critical flicker frequency is reduced in multiple sclerosis patients independently of retinal axonal damage

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**Background:** Critical flicker frequency (CFF) has been suggested as a marker for neuro-axonal damage resulting from demyelinating optic neuritis (ON). Neuro-axonal damage of the retina is frequently observed in patients with multiple sclerosis.

**Objective:** To examine CFF in eyes with and without ON (NON) of MS patients and eyes of healthy controls (HC) and to further investigate possible associations with visual function as well as with the Expanded Disability Status Scale (EDSS).

**Methods:** A total of 140 eyes from 39 MS patients (28 ON-eyes; 50 NON-eyes) and 31 HC were evaluated. All patients and HC underwent monocular and binocular CFF measurements with the HEPAtonorm™-Analyzer, monocular high contrast visual acuity (HCVA) testing with ETDRS charts (logMAR units), binocular low contrast letter acuity (LCLA) testing with 2.5% contrast Sloan charts, visual evoked potentials (VEP) and spectral domain optical coherence tomography (OCT) with analysis of the peripapillary retinal nerve fibre layer (pRNFL) thickness. Trained neurologists assessed the EDSS for all patients. Monocular measurements were analyzed with generalized estimating equations (GEE), binocular measurements with t-test and Spearman correlation analysis.

**Results:** Mean monocular CFF for eyes of MS patients amounted to  $40.9 \pm 4.4$  Hz and was significantly lower than in HC ( $44.8 \pm 4.4$  Hz,  $p < 0.001$ ). Worse EDSS was a moderate predictor for reduced CFF

( $r^2 = 0.261$ ,  $B = -2.060$ ,  $p < 0.001$ ). In contrast, there was no significant difference in CFF between ON-eyes ( $39.7 \pm 5.2$  Hz) and NON-eyes ( $41.5 \pm 4.3$  Hz,  $p = 0.127$ ). Likewise, there was no association between CFF and pRNFL thickness ( $B = 0.009$ ,  $p = 0.750$ ). CFF was mildly associated with VEP P100 latency ( $r^2 = 0.069$ ,  $B = -0.056$ ,  $p = 0.043$ ), HCVA ( $r^2 = 0.074$ ,  $B = -6.021$ ,  $p = 0.002$ ) and LCLA

( $r^2 = 0.120$ ,  $p = 0.41$ ,  $p = 0.010$ ).

**Conclusion:** CFF reduction in MS occurs independently of ON, and is not dependent on retinal axonal damage. Its moderate correlation with EDSS suggests that CFF potentially reflects global disease processes or higher cortical processing and neurodegeneration rather than focal optic nerve damage.

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### EP1394

#### Long-term predictors of disability worsening in patients with multiple sclerosis in the phase 3 TRANSFORMS study

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**Background:** In patients with multiple sclerosis, disease and treatment history, early magnetic resonance imaging (MRI) lesion activity, and/or relapses may predict long-term clinical outcomes.

**Objectives:** To assess the ability of variables at baseline and during the 1-year TRANSFORMS trial to predict long-term disability worsening during the study extension.

**Methods:** This was a *post hoc* analysis of data from the 36-month follow-up to the randomized, double-blind TRANSFORMS study comparing fingolimod and intramuscular (IM) interferon (IFN) beta-1a. During follow-up, patients randomized to IFN beta-1a IM were switched to fingolimod. Multiple logistic regression was used to assess which patient or disease characteristics from baseline to month (M) 12 predicted two disability outcome measures (6-month confirmed disability progression [6MCDP]; Expanded Disability Status Scale [EDSS] score  $>6$ ) during M12–48. Baseline variables included sex, age, duration of MS since diagnosis, previous treatment for MS, number of relapses in the previous 2 years, EDSS score, number of gadolinium-enhancing [Gd+] lesions, T1 hypointense volume and total volume of T2 lesions. Baseline to M12 variables included the number of confirmed relapses, EDSS score change, presence of new T2 lesions and presence of MRI lesion activity.

**Results:** In total, 1292 patients were randomized in TRANSFORMS (analysis sets for the multiple regression analysis: 6MCDP,  $n=758$ ; EDSS score  $>6$ ,  $n=934$ ). Predictors of both outcomes were baseline EDSS score (odds ratio [95% confidence interval]: 6MCDP: 1.353 [1.138-1.609],  $p=0.0006$ ; EDSS score  $>6$ : 3.335 [2.530-4.396],  $p<0.0001$ ) and the presence of MRI lesion activity during M0-12 ( $\geq 1$  Gd+ or  $\geq 2$  new T2 lesions, 6MCDP: 1.854 [1.038-3.310],  $p=0.0369$ ; EDSS score  $>6$ : 3.434 [1.292-9.128],  $p=0.0134$ ). Change in EDSS score during M0-12 (2.794 [1.990-3.921],  $p<0.0001$ ) and T1 hypointense lesion volume at baseline (1.297 [1.082-1.555],  $p=0.0049$ ) were predictors of EDSS score  $>6$  only.

**Conclusions:** In TRANSFORMS, baseline EDSS score and MRI lesion activity during

M0-12 were predictors of both disability outcomes in the long term. Change in EDSS score during M0-12 and T1 hypointense lesion volume at baseline were predictors of patients reaching an EDSS score  $>6$ . These findings support early review of treatment regimens to help to prevent worsening disability.

### Disclosure

**Pavle Repovic:** Acorda Therapeutics, Biogen Idec, EMD Serono, Genzyme, Novartis Pharmaceuticals Corporation, Pfizer and Teva Pharmaceuticals (multiple sources).

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### EP1395

#### Modified brief international cognitive assessment for multiple sclerosis (mBICAMS): towards validating the first Arabic version

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**Background:** Cognitive performance is a sensitive indicator of disease progression in Multiple Sclerosis (MS). The BICAMS psychometric characteristics have not been established in Arabic-speaking populations.

**Objective:** To validate and provide normative and psychometric data for the BICAMS in Arabic.

**Methods:** In this cross sectional study, mBICAMS will be administered to 184 healthy subjects with no history of neurological disorders, traumatic brain injury, psychiatric disorders, and cognitive impairment, aged 16-90 years [ $n=62$ ; age 16-35,  $n=72$ ; 36-65,  $n=50$ ; 66-90 years], and 50 MS patients. Additional screening using the Hopkins Symptom Checklist-25 (depression score  $\leq 3.3$ ,

excluded) and Montreal Cognitive Assessment (score  $< 26$ , excluded) is performed. mBICAMS consists of 3 tests; the Symbol Digit Modalities Test (SDMT), the Brief Visuospatial Memory Test-Revised (BVMTR), and a newly developed Verbal Memory Arabic Test (VMAT) - a learning test of 15 culturally sensitive words, consisting of five learning trials, immediate and delayed trials, with and without cues, and a recognition trial). Cognitive reserve and non-verbal intelligence quotient are also assessed. The BICAMS validation method is based on Benedict et al. 2012<sup>7</sup> recommendations.

**Results:** To date, 93 participants were screened (10 excluded; for drug dependence, psychiatric disorders, antidepressant use, or high depression score, and 5 participants dropped out). Of these participants, 77 healthy subjects (43 females and 34 males) and 1 MS patient completed the study, and retest has been performed on 45 of these subjects after 21 days on average (M age  $29.5 \pm 10.8$  years). Most participants (80%) obtained medium cognitive reserve scores (M  $105.86 \pm 12.78$ ), and showed average nonverbal intelligence quotient ( $105.78 \pm 16.03$ ). SDMT yielded  $61.38 \pm 8.96$  correct answers (test-retest  $r=0.64$ ). On the VMAT, mean number of words recalled on the first 5 learning trials was  $10.99 \pm 1.49$ , short delay recall  $11.23 \pm 2.29$ , cued recall  $11.53 \pm 2.15$ , long delay recall  $11.88 \pm 2.29$ , cued recall  $11.99 \pm 2.24$ , recognition trial  $43.45 \pm 1.98$  out of 45 words). VMAT showed acceptable test-retest reliability;  $r=0.43$ . On the BVMT-R, participants scored  $5.42 \pm 2.42$  on trial 1,  $8.75 \pm 2.42$  trial 2, and  $10.42 \pm 1.88$  trial 3 (test-retest Cohen's  $d=1.15$ ).

**Conclusions:** Recruitment and data collection are ongoing. Validating the mBICAMS will allow more accurate clinical use and research utilizations of these measures in the Arab world MS patients.

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### EP1396

#### Body worn sensors accurately and reproducibly quantify disability and walking impairment in a clinical setting in people with MS

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**Introduction:** Accurate quantification of disability in people with MS is becoming increasingly relevant. In clinical care the discovery

of disease modifying therapies with impact on progressive MS requires accurate serial assessment of disability to assess eligibility and clinical effect<sup>1</sup>. In research there is an unmet need for reliable clinical measures that would be expected to change over the 2-3 year life span of a progressive MS trial<sup>2</sup>. Expanded Disability Status Scale (EDSS) has proven to be both insensitive and unreliable to these tasks<sup>3</sup>. Body-worn sensors offer the potential of a sensitive, objective and reproducible measure of a walking disability.

**Aims:** We investigated whether data from body worn sensors would be able to distinguish between controls, people with MS with moderate disability (EDSS 2.5-5.0) and people with MS with more advanced disability (5.5-6.5), whether the data was reproducible and whether parameters correlated with current validated measures.

**Method:** 69 patients with MS and 24 age and gender matched healthy controls participated in the study. Participants completed a 10m Walk, Instrumented Timed-Up-And-Go (iTUG), Instrumented Sway (iSway) and six-minute walk (6MW) on two separate visits.

**Results:** Sensor measures captured during the 10m Walk, iTUG and 6MW showed significant difference between the three groups ( $p < 0.001$ ). Sensor data showed high reliability with excellent reproducibility across most of the walking parameters ( $ICC > 0.75$ ). Many parameters showed significant correlations (varying from strong to moderate) with validated measures. Particularly strong correlations were found between the walking parameters and EDSS.

**Conclusion:** Body-worn sensors offer a highly reproducible and sensitive way of disability in people with MS. They show potential for implementation into clinical practice as well as clinical trials as a measure of disability progression.

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## EP1397

### Can MS patients accurately self-time the 25-foot walk?

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Schindler<sup>3</sup>, J. Alberts<sup>3</sup>, R. Rudick<sup>4</sup>, G. Phillips<sup>4</sup>, J. Rhodes<sup>4</sup>, S. Rao<sup>1</sup>

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**Background:** The MS Performance Test (MSPT), a self-administered iPad®-based neurological performance assessment tool, is designed to be integrated into routine clinical care. One of the MSPT test modules, the Walking Speed Test (WST), allows MS patients to self-time their walk along a 25 foot track. Typically, the 25-Foot Walk is timed by a technician using a stopwatch. For the MSPT WST, patients click a hand-held Bluetooth button at the start and stop of their walk; time is recorded on the iPad.

**Goals:** To determine if self-timed walking speed is as accurate, sensitive and reliable as technician timed walking speed.

**Methods:** The participants consisted of 30 MS patients (course: 25 relapsing remitting, 3 secondary progressive, 2 primary progressive; disease duration: mean=8.3 yrs, SD=7.7) and 29 healthy controls (HC). The two groups were equivalent in age (MS: mean=45.6 yrs, SD=11.6; HC: mean=46.3 yrs, SD=10.4), education (MS: mean=15.2 yrs, SD=2.7; HC: mean=15.7 yrs, SD=2.3), and sex (MS: 20 females; HC: 19 females). Both groups of subjects completed the WST twice on the same day. A technician simultaneously timed their walk with a stopwatch.

**Results:** As expected, MS patients had significantly slower walking times than the HC group both for the self-timed ( $p=0.02$ ; Cohen's  $d$  effect size=.660) and technician-timed ( $p=0.01$ ; Cohen's  $d$ =.708) latency measures. Absolute differences between the self-timed and technician-timed measures were small and comparable (MS, mean=0.48 sec.; HC, mean=0.37 sec.;  $p=0.285$ ). Correlations between self-timed and technician-timed walking speeds were high and comparable (MS,  $r=0.943$ ; HC,  $r=0.928$ ). Test-retest reliability was high and comparable for the self-timed (MS,  $r=0.931$ ; HC,  $r=0.854$ ) and technician-timed (MS,  $r=0.977$ ; HC,  $r=0.927$ ) measures.

**Conclusions:** These results validate the use of self-timed walking speed measures for both MS patients and healthy individuals. Compared to technician-timed latency measures, self-timed measures were equally sensitive in detecting differences in walking speed between MS and HC groups. Absolute latency differences and test-retest reliability were comparable for the self-timed and technician-timed measures for both MS patients and healthy controls. Because it is self-administered, the WST, as part of the MSPT battery, has the advantage of being integrated into clinical practice without involving clinic personnel.

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#### EP1398

##### **The use of a mobile-phone-based E-diary for evaluation of patient-reported outcomes and adherence to treatment of patients with multiple sclerosis**

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**Background:** Little is known regarding the applicability of smartphone technology to promote clinical care of patients with Multiple Sclerosis (PwMS).

**Aim:** To assess the usefulness of a smartphone-based e-diary to the estimation of adherence to disease modifying drugs (DMDs), as well as to the collection of patient-reported outcomes (PROs).

**Methods:** Patients downloaded a MS tailored e-diary into their personal smartphones. The application prompted patients to take their DMDs and recorded their adherence. Report of PROs was conveyed once monthly through the application, using previously validated tools (Multiple Sclerosis Quality of Life inventory, Neuro-QoL short forms and CNS lability scale). Adherence data from the e-diary was compared to medication pack collection. PROs gathered by the e-diary were compared to corresponding functional system scores, determined by neurologic examination, as well as to patients' subjective reports during routine follow up visits, as documented in their electronic medical record (EMR).

**Results:** Data from 83 PwMS was used in this analysis [Female: 54 (65%), EDSS 3.4±2.1]. Patients were using the e-diary for a median duration of 17 weeks [range:4-29 weeks]. Only 7 patients (8%) dropped out and another 3 (3%) did not agree to participate in PRO survey but continued to report their medication intake. Adherence to DMDs as reported in the e-diary was 87.1±17.8% compared to 84 ±19.2% according to pack collection. E-diary derived PROs were significantly correlated with the corresponding functional system scores ( $0.46 < r < 0.8$ ,  $P < 0.0001$ ). The E-diary captured more MS related symptoms than documented in the EMR (e-diary compared to EMR: poor sleep 49% vs. 5%, pseudobulbar affect 17% vs 3%, upper limb dysfunction 10% vs 3% of participants). In patients with a relapse we noted increased PRO scores, which decreased following remission.

**Conclusion:** Smartphone-based e-diary seems suitable for PwMS and can provide useful information regarding PROs and adherence to DMDs.

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#### EP1399

##### **QuantemTool - automated measurement of lesion load and cerebral volume from magnetic resonance images in multiple sclerosis**

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**Background:** In multiple sclerosis (MS), brain magnetic resonance imaging (MRI) is the standard method for evaluating and monitoring brain lesions. Conventional MRI lesion measures only modestly predict disability. There is an increasing amount of research correlating brain tissue loss, in particular grey matter (GM) atrophy, to clinical disability, suggesting the need of quantitative analyses of MRIs in clinical practice.

QuantEmTool (QET) is an automated tool based on a standard analysis pipeline that segments the brain and quantifies its main structures, also quantifying lesion load volumes.

The main goal of this work is to evaluate whether QET results, as correlated with clinical data, are in line with related published studies, hence contributing to support its use in clinical practice.

**Methods:** We selected all consecutive patients with a MS or Clinical isolated syndrome (CIS) who performed an MRI since January 2016. Correlations between MRI parameters (grey matter (GM), parenchymal volume (PV), white matter (WM) and T2 lesion volume (T2LV)) and clinical variables (age, disease duration, Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Severity Score (MSSS)) were estimated using Pearson's correlation coefficient (R), and multiple regressions.

**Results:** 27 females and 24 males, from 19 to 60 years (mean 42) and mean age of disease onset at 32 years were analysed; 1 patient with clinically isolated syndrome, 43 patients with relapsing-remitting MS, 1 patient with secondary progressive MS and 4 patients with primary progressive MS, were included.

There was a negative correlation between brain atrophy parameters and disability: between GM and EDSS and MSSS respectively  $R=0.54$  ( $p < .001$ ) and  $R=0.37$  ( $p=0.01$ ); between PV and EDSS and MSSS respectively  $R=0.49$  ( $p < .001$ ) and  $R=0.30$  ( $p=0.03$ ). MRI parameters of atrophy are also correlated with age and disease duration, as well as with T2LV ( $R=0.50$  ( $p < .001$ ) for SC). An even stronger correlation with EDSS was disclosed combining patient's age with PV and namely with SC ( $R=0.64$ ;  $R^2=0.41$ ;  $p < .001$ ).

**Discussion:** These results suggest that MRI parameters of brain atrophy are correlated with the disability degree of MS patients. Additionally, grey matter atrophy seems to have a stronger correlation with disability than whole brain atrophy. This is also in line a variety of recent studies suggesting that GM atrophy could be a more sensitive marker of disease progression in MS.

## Disclosure

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## EP1400

### Validation of a clinical risk score for long-term progression of MS

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**Introduction:** Reducing risk of multiple sclerosis (MS) progression is a challenge in the MS treatment. The application of the clinical risk score to predict long term progression is useful and has been little explored.

**Objective:** To validate a clinical risk score (CRS) for long-term severity based on demographic and clinical factors present in the disease onset.

**Methods:** CRS-MS was derived based on five factors identified as more significant after a Cox regression model analysis in 150 patients with ten or more years of the disease. African ancestry, age onset above 30 years, two or more relapses at first year of the disease, pyramidal and cerebellar impairment as first manifestation, and to have EDDSS 3 before the first treatment were identified as independent variables that influence the time to reach progression. The numerical value of 1.0 was given to all factors because hazard ratios (HR) and beta coefficients had close values. The sum of the single scores gives the overall risk score. In the second phase, we validated the score: The CRS-MS was applied in another 270 patients with at least two years of the disease duration.

**Results:** Progression was observed in 21% (57/270), with mean disease duration of 19.07 years (4-47; SD± 10.6 years). Among these patients, 66% percent had three or more clinical risk factors and the risk for progression was 14.3 (95% CI 7.2-28.4,  $p < 0.001$ ). All patients with none factor were progression free.

**Conclusion:** The CRS-MS was able to predict the risk of long-term progression to patients with two or more years of disease, and it can assist in the choice of an early treatment and individualized to avoid long-term disability.

## Disclosure

nothing to disclose

## EP1401

### Novel integrative approach combining patient, physician and empirical assessments for diagnosing secondary-progressive multiple sclerosis

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**Background:** Diagnosis of secondary-progressive multiple sclerosis (SPMS) is challenging due to active and non-active progressive phases, following an initial relapsing course. To support timely diagnosis, a screening tool was previously developed based on qualitative interviews with patients and physicians, and data from a real-world observational study.

**Objective:** To create a scoring algorithm for the newly developed screening tool to support physicians in the diagnosis of SPMS.

**Methods:** Multiple logistic regression analyses were performed on observational study data ( $n=2791$ ) to identify predictive variables for SPMS. Qualitative interviews ( $n=8$ ) were conducted to determine physician-perceived importance of variables for progression to SPMS. Additional variables were identified in qualitative interviews apart from those included in the observational study. Ranking

(1–26; 1=most important) and weighting (%) outputs were analysed by descriptive statistics; interview transcripts were qualitatively analysed. Variables of high, moderate or low importance were integrated in the algorithm. Concordance levels among physicians were assessed by Kendall's coefficient.

**Results:** Regression analyses identified mobility (odds ratio, 4.457,  $p < 0.0001$ ) and self-care (2.388;  $p < 0.0001$ ) as the strongest patient-reported predictors. Expanded Disability Status Scale score (1.789;  $p < 0.0001$ ), age (1.037;  $p < 0.0001$ ) and MS disease activity (1.681;  $p < 0.05$ ) were identified as the most significant physician-reported predictors. In physician interviews, the most important variables were stability/worsening of symptoms (average weighting [range]; average rank: 11% [1–33%]; 5), intermittent/persistent symptoms (7% [0–17%]; 7) and presence of ambulatory symptoms (7% [0–15%]; 8). Moderately important variables included signs of new magnetic resonance imaging activity (6% [0–20%]; 14), recovery from last relapse (5% [0–12%]; 13) and impact on daily activities (5% [1–10%]; 13). Presence of fatigue, visual symptoms and impact on hobbies/leisure time were considered less important (2% [0–10%]; 16–19). Overall, concordance levels among physicians were significantly low to moderate (0.278;  $p=0.0004$ ); greater agreement was observed within countries (US: 0.522, Germany: 0.385;  $p < 0.01$ ).

**Conclusions:** Findings confirm the need for a prognostic tool to support early identification of SPMS. This is the first algorithm that integrates patient, physician and empirical assessments to be developed for clinical validation.

## Disclosure

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**Bryan Bennett, Chloe Tolley and Sarah Kilgariff** are employees of Adelphi Values, Macclesfield, UK.

**Davorka Tomic** and **Daniela Piani Meier** are employees of Novartis.

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#### EP1402

##### **Biological rhythms in MS patients with mood disorders: what impact on quality of life?**

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**Background:** Multiple Sclerosis (MS) is a chronic neurological disease that mainly affects young adults, adversely impacting on many aspects of their life. Notoriously, mood disorders may be associated with abnormalities in biological rhythms (BR), with changes in sleeping and eating patterns as well as in social and daily activities. Psychiatric comorbidities are very common among MS patients (Carta et al., 2014), while the presence of dysregulation of BR has not been adequately explored.

This study aimed to investigate the relationships between circadian BR disturbance with MS clinical features and psychiatric comorbidity. In addition, we evaluated the weight of BR impairment on patients' quality of life (QoL).

**Methods:** MS patients, diagnosed according to McDonald criteria, were enrolled and clinical features were collected.

DMS IV psychiatric diagnoses were determined by ANTAS-SCID interview (Carta et al., 2010).

The Italian Version of the BRIAN questionnaire was used to assess abnormalities in BR (sleep, eating, activities and social rhythms) (Moro et al., 2010). QoL was evaluated with the Short Form Health Survey (SF-12) (Ware et al., 1996). Descriptive statistics, hierarchical regression analyses, t-test, and the Pearson's correlation were conducted.

**Results:** The sample included 178 MS patients (61 male); of these 38/178 had progressive course. Mean value for the disease duration was 10.5 years, while mean EDSS was 2.5. The diagnosis of unipolar depression was established in 43/178 (24.1%) patients, and bipolar spectrum disorders in 32/178 (17.9%). BRIAN scores were respectively 43.6 and 34.4 in patients with and without mood disorders ( $p < 0.001$ ). Psychiatric comorbidity, in particular bipolar disorder, was the strongest determinant of BR dysregulation ( $p < 0.01$ ), independent from MS clinical features (EDSS and disease duration). However, an association between BR impairment and EDSS score was observed ( $p < 0.01$ ). In addition, BRIAN score was negatively associated with SF-12 score ( $r = -0.529$ ;  $p < 0.001$ ).

**Conclusions:** Psychiatric comorbidities seem to strongly influence BR dysregulation in people living with MS. BRIAN questionnaire could be a useful tool in clinical practice to identify BR abnormalities also in MS, bearing in mind the impact of these abnormalities on QoL as well as their association with psychiatric comorbidities.

**Keywords:** biological rhythms abnormalities; BRIAN questionnaire; psychiatric comorbidities; quality of life.

#### **Disclosure**

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Dr. Fenu received honoraria for consultancy from Novartis and for speaking from Merck Serono and Teva.

Dr. Frau serves on scientific advisory boards for Biogen, received honoraria for speaking from Merck Serono and Teva.

Dr. Coghe received speaker fee from Teva and Almirall.

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Mrs Pitzalis and Professor Carta have nothing to disclose.

#### EP1403

##### **How do people with multiple sclerosis feel about MRI?**

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**Background:** Magnetic resonance imaging (MRI) is frequently applied in diagnosis, prognosis and therapy monitoring of multiple sclerosis (MS). MS-patients regularly undergo MRI scanning and are therefore constantly confronted with MRI results and images. But little is known about MS-patients' knowledge of and attitude towards MRI. We hypothesized that MS patients would rate their MRI results as very important and that relevant anxiety is associated with the scanning and delivery of results. Fear of MRI-results might diminish with longer disease duration, higher number of MRI scans as well as higher knowledge about MRI.

**Objective and methods:** An online survey was conducted among  $n=498$  MS-patients in November/December 2016 via the website of the German MS-society.  $N=388$  MS-patients answered a 23-item MRI-risk knowledge questionnaire (MRI-RIKNO) based on earlier work (Brand et al. 2014).  $N=490$  patients answered an MRI-emotions and attitude questionnaire (MRI-EMA), in which participants rated 17 statements about MRI (e.g. „My last MRI result was very important to me.“) on Likert scales. Chi-Q-test was used to examine differences between patient subgroups.

**Results:** The majority of participants were female (70%) and had a relapsing-remitting MS (RRMS) course (80%). Mean age was 43, MS was diagnosed between 1975 and 2016 and mean disease duration was 8 years. The average score in the MRI-RIKNO was 15/23 correctly answered questions (65%). MRI-results were very important to the majority of patients (55%), but importance seemed to fade when transition to secondary MS had been reached (35% versus 60% in both RRMS or primary-progressive MS (PP-MS)). Almost all patients wished to discuss their results with a radiologist/neurologist (80%), however 25% did not at all feel competent to do so. The MRI scan itself was not stressful to the majority of patients (50%), but a third of patients declared that they were anxious before having received their most recent MRI-results. This fear seemed to diminish with longer duration of the disease (MS-diagnosis  $< 5$  years: 40%, MS-diagnosis 20 to 30 years: 20%) and higher number of MRI-scans ( $< 5$  MRI-scans: 40%,  $> 10$  MRI-scans: 20%).

**Conclusion:** MRI is very important to the majority of MS patients, but MRI knowledge is only modest. The MRI results, but not the



procedure itself, are associated with anxiety. This anxiety inversely correlates with disease duration as well as number of MRIs.

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### EP1404

#### Clinical validity of EDSS and SDMT in the detection of MS disease activity

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**Introduction:** Relapse rate and changes in MRI and the Expanded Disability Status Scale (EDSS) are universally used as indicators of therapeutic efficacy in disease modifying treatments in multiple sclerosis (MS). Though, the EDSS has limitations, namely, in the assessment of cognitive dysfunction.

**Objective:** To investigate the accuracy of clinical measures in the detection of disease activity.

**Methods:** Patients with MS were evaluated using clinical and MRI measures in two different moments. Disease activity was defined as  $\geq 1$  relapses and/or changes in MRI ( $\geq 2$  Gd-enhancing or new T2 lesions). It was considered a change ("clinically meaningful worsening") if EDSS $\geq 1$ , Timed 25-foot walk (T25FW)  $\geq 20\%$ , 9-hole peg test (9HPT)  $\geq 20\%$ , and symbol digit modality test (SDMT)  $\geq 10\%$ . Classification accuracy statistics and Fisher's exact were applied.

**Results:** Of the 132 patients included (67% females, age=42 $\pm$ 11, education=14 $\pm$ 6, disease duration=12 $\pm$ 7 years; first evaluation EDSS=2.6 $\pm$ 3.4, 85% were under disease modifying treatment and time between evaluations=12 $\pm$ 5 months), 43 (33%) met the criteria for disease activity. Changes in EDSS and SDMT correctly classified (sensitivity) respectively 23/43 (54%) and 26/43 (61%) patients with disease activity. However, there was a modest association between changes in EDSS and SDMT ( $p=0.029$ ; 34/132 patients had changes in one measure but not on the other). When combined, the sensitivity and specificity of EDSS and SDMT reached respectively 93% and 97%. The sensitivity of changes in T25FW (16%) and 9HPT (5%) was low.

**Conclusion:** Changes in EDSS and SDMT have high accuracy in the detection of disease activity. Though, these clinical measures may be sensitive to different aspects of disease activity.

### Disclosure

Nothing to disclose

### EP1405

#### Optimizing standards of approach in multiple sclerosis result in better outcomes. A Brazilian open label study on quality of care

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**Objective:** A critical analysis on whether optimization of approach and follow up in relapsing remitting MS (RRMS) patients impact long term outcomes in real world scenario.

**Background:** Multiple sclerosis (MS) treatment evolved on last two decades, mostly after introduction of so called disease modifying drugs (DMDs). Parallel to advent of new drugs our expertise applying diagnostic protocols and custom therapy improved. Nevertheless, paradigms for optimal care in MS still depend upon prompt and correct diagnosis together with an early as possible onset of treatment.

**Design and methods:** Consecutive naive RRMS patients (McDonald 2001), all using a first line DMD, were stratified according to year of inclusion on treatment program, from 2002 to 2004 (n=101), 2005 to 2007 (n=93) and 2008 to 2010 (n=128). There were 17

treatment discontinuations: 9 in first, 6 in second and 2 in third cohort. Intention-to-treat data were plotted after 4 years in each group.

**Results:** Cohorts matched for age, gender, age at first relapse, prior annualized relapse rate (ARR) and time from first to second relapse. On baseline, time delay to beginning of DMD ( $p<.0001$ ) and number of T2W hyperintense MRI lesions ( $p<.01$ ), were significant especially when comparing cohorts 1 and 3. Annual number of visits ( $p<.001$ ) and frequency of imaging studies ( $p<.001$ ) were also noteworthy. On follow up, ARR ( $p<.0001$ ), EDSS worsening more than 1 point confirmed at 6 month ( $p<.0001$ ), NEDA 3 (no relapses, no Gd+ and/or new T2W lesions, no EDSS progression) ( $p<.0002$ ) and annualized corpus callosum index (CCI) loss ( $p<.001$ ) was also relevant. All differences had more impact when comparing first and third cohorts.

**Conclusions:** Prompt and early institution of treatment had a positive impact on inflammation (ARR and NEDA3) as well as a possible benefit on degenerative domain (EDSS and CCI). Our findings suggest that optimization of standards of care can positively impact on long term disease course.

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### EP1406

#### Histologic validation of rapid myelin detection using quantitative MRI

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**Background:** Myelin detection is of great value in monitoring Multiple Sclerosis, both for global assessment of brain atrophy as for local probing of brain tissue integrity in e.g. DAWM or perilesional tissue. Most MRI methods to measure myelin, however, are impractical to perform in clinical routine due to excessive scan or post-processing times. Recently, a novel method was published, where the presence of myelin is inferred using its effect on the intra- and extracellular water relaxation rates and proton density, observable by rapid quantitative MRI. The method provides high-resolutions myelin maps in about 5 minutes scan time and 10 seconds post-processing time. The purpose of this work was to validate this method further using comparison with gold-standard histology.

**Materials and methods:** The brains of 12 fresh, intact cadavers were scanned with the quantitative MRI sequence. R1 and R2 relaxation rates and proton density PD, as well as myelin maps were automatically calculated using SyMRI (SyntheticMR, Sweden). Subsequently, the brains were excised at autopsy and brain slices were stained with Luxol Fast Blue to verify the presence of myelin. The stained brain specimens were photographed and converted to optical density maps. The LFB optical density maps were registered and correlated with the qMRI myelin maps.

**Results:** A correlation was found between the two methods with a mean Spearman's correlation coefficient for all subjects of  $0.74 \pm 0.11$ . Linear regression showed a mean intercept of  $1.50 \pm 2.84\%$  and a mean slope of  $4.37 \pm 1.73\%/\%$ .

**Conclusion:** The observed correlation with LFB histology supports the validity of myelin measurement using rapid quantitative MRI. Rapid, automatic myelin measurements may improve quantitative monitoring of MS patients.

## Disclosure

MW is part-time employed at SyntheticMR AB

## EP1407

### Health-related coping and social interaction in people with multiple sclerosis supported by a social network: a pilot study with a new methodological approach

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**Background:** Social media are a vital link for people with Multiple Sclerosis (pwMS) who find in web-communities a comforting source for information exchange, debates and knowledge enrichment. PwMS are well informed about the disease but are vulnerable to hopes of being cured or saved by therapies whose efficacy is not always scientifically proven. To overcome this issue, we created an MS experts social network (SMSocialnetwork.com), guaranteeing a constant online presence of the medical team to oversee and participate on the public wall and intervening

promptly in case of posts with false or inappropriate medical information.

**Objective:** To assess the impact of SMSocialnetwork.com on pwMS health-related coping and social interaction analyzing the areas of interest through a web-based survey.

**Methods:** Referring to previous marketing studies analyzing the online platforms role in targeted healthcare, we conducted a 39 item web-based survey. To investigate health related coping and social interaction in pwMS we performed a construct validation procedure, with a factorial analysis, gathering together akin items of the survey, related of the following areas of interests: "utility", "proximity", "sharing", "interaction", "solving uncertainty", "suggestion attitude" and "explore".

**Results:** We collected 130 web-based survey. Our analysis demonstrated that the users-pwMS (UP) positively evaluated SMSocialnetwork.com to

- obtain information, approach and solve problems and to make decision ("utility": median 4,2)
- improve feeling of closeness ("proximity": median 5)
- catalyze relationship ("sharing": median 5.6)
- get in touch with other users to receive innovative, effective and practical solutions ("interaction", "solving uncertainty" and "suggestion attitude" medians were, respectively: 4.1, 3 and 3)
- share information about innovative therapeutic approaches and treatment options ("sharing": median: 5.3).

**Conclusion:** SMSocialnetwork was perceived by UP as a useful tool to support health-related coping and social interaction, and may suggest a new kind of therapeutic alliance between physicians and pwMS.

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## EP1408

### Reliable cross-sectional correlations between a visual rating brain atrophy scale and quantitative MRI volumetric measures in multiple sclerosis

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**Background:** Measuring whole brain atrophy has become a topic of interest in the clinical assessment of multiple sclerosis (MS). Conventional magnetic resonance imaging (MRI) in the real clinical setting may suggest the degree of cross-sectional whole brain

atrophy. The generalized Pasquier scale (four-step) is simple, and is one of the main visual brain atrophy scales used for neuroradiologists in order to give a semi-quantitative insight on the axonal degeneration in MS patients.

**Goal:** In this study we aim to assess the correlations between the generalized Pasquier scale and quantitative automated MRI volumetric measures.

**Method:** Thirty-seven patients with MS were recruited from the MS Clinic at the Hospital Clínico de la Universidad de Chile (recurring-relapsing MS 78%, clinically isolated syndrome 22%). They were assessed by conventional MRI imaging; semi-quantitative whole brain atrophy assessment was performed by two neuroradiologists using the generalized Pasquier scale. Cross-sectional Structural Imaging Evaluation with Normalization of Atrophy (SIENAX) analysis was performed in order to assess the global brain volume, and its partitions of grey matter - matter, peripheral grey matter and ventricular volume.

**Results:** The mean age was 32.4 years (range 18-52), 70% female, disease duration 1.7 years (0.7 -7), baseline Kurtzke EDSS 1.4 (0-4). There was 10.8% of patients without cortical atrophy according to generalized Pasquier scale, mild atrophy 51.4%, moderate 35.1% and severe 2.7%. These categories correlated positively well with the ventricular volume ( $r: 0.74; p < 0.001$ ), and negatively well with the whole brain volume ( $r: -0.51, p = 0.001$ ), peripheral grey matter volume ( $r: -0.45, p = 0.005$ ), white matter volume ( $r: -0.47, p = 0.003$ ), and the total grey matter volume ( $r: -0.42, p = 0.009$ ).

**Conclusion:** These results suggest that a semi-quantitative assessment using a visual rating of brain atrophy scale correlates well with the automated volumes that SIENAX provides. This may be useful when assessing the baseline profiles in MS patients in the real clinical practice in order to select the first disease-modifying agent.

## Disclosure

nothing to disclose

## EP1409

### Association between perceived fatigue and balance measured by posturography in patients with multiple sclerosis

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**Background:** Fatigue is one of the most common symptoms seen in about 80% of patients with Multiple Sclerosis (MS). It is known that imbalance that affects physical performance are closely related to symptoms such as fatigue, but the relationship between fatigue and balance is not yet clear in patients with MS.

**Objective:** The purpose of this study was to investigate the effect of fatigue severity on balance in patients with MS.

**Methods:** Participants: Forty-one ambulatory patients with MS (Age: 36.46 ± 8.61 years, EDSS: 1.62 ± 1.06) participated in the study.

**Main measures:** Fatigue was assessed using the self-report Fatigue Severity Scale (FSS). Balance was assessed using the Biodex Balance System which included the postural stability test, the limit of stability test, and the sensory organization test. In the postural

stability test, the patients were asked to stand for 30 seconds on both feet and 10 seconds each on one foot. In the sensory organization test, the patients were asked to stand on both feet under four altered sensory conditions (1. Eyes open-firm surface, 2. eyes closed-firm surface; 3. Eyes open-foam surface, 4. Eyes closed-foam surface). In the limit of stability test, the patients were asked to reach to 8 predetermined target positions in the forward, backward, rightward, leftward, forward-rightward, forward-leftward, backward-rightward, and backward-leftward directions

**Statistical analysis:** Spearman correlation analysis was used to determine relationships between balance and fatigue.

**Results:** In patients with MS, the fatigue severity was associated with the postural stability scores on both feet ( $r: 0.391, p: 0.011$ ); on right foot ( $r: 0.398, p: 0.01$ ); on left foot ( $r: 0.351, p: 0.024$ ), and was associated with the sensory organization test scores under all condition ( $r: 0.379-0.537, p < 0.05$ ). The fatigue severity was associated with the limit of stability score in only the backward direction ( $r: -0.358, p: 0.021$ ), but not associated with the limit of stability in others directions ( $p > 0.05$ ).

**Conclusion:** This study showed that postural sway and fatigue affect each other negatively. More effective results can be obtained by adding fatigue management strategies and balance exercises to the rehabilitation program in patients with MS.

## Disclosure

There is no conflict of interest and funding in this study.

## EP1410

### Effect of physical activity level on functional exercise capacity in patients with multiple sclerosis

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**Background:** Both functional exercise capacity, and physical activity level decrease in patients with Multiple Sclerosis (MS). Which physical activity domains are associated with functional exercise capacity is not yet clear in patients with MS.

**Objective:** The purpose of this study was to examine the effect of physical activity domains on the functional exercise capacity in patients with MS.

## Methods:

**Participants:** Forty-one ambulatory patients with MS (Age: 36.46 ± 8.61 years, EDSS: 1.62 ± 1.07) participated in the study. **Main Measures:** The International Physical Activity Questionnaire (IPAQ) was used to measure total physical activity domains including leisure time, domestic and gardening (yard) activities, work-related, and transport-related activity over the last 7 days. In addition, the total scores for the each activity type including walking, moderate-intensity activities, and vigorous-intensity activities were calculated by using the answers given to these domains. Functional exercise capacity was assessed with the six-minute walking test (6MWT) and walking distance was recorded as the meter.

**Statistical analysis:** Spearman correlation analysis was used to determine relationships between physical activity and functional exercise capacity.

**Results:** In patients with MS, the functional exercise capacity was associated with domestic and gardening activity level ( $r: -0.379$ ,



$p=0.015$ ), work-related activity level ( $r: 0.409$ ,  $p=0.008$ ), walking activity level ( $r: 0.334$ ,  $p=0.033$ ), and vigorous-intensity activity level ( $r: 0.452$ ,  $p=0.003$ ).

**Conclusion:** This study demonstrated that while the work-related, the walking, and the vigorous-intensity activities are positively associated with the functional exercise capacity, the domestic and gardening activities are negatively associated with functional exercise capacity. Therefore, functional capacity can be improved by increasing physical activity level in patients with MS.

### Disclosure

There is no conflict of interest and funding in this study.

### EP1411

#### A longitudinal study correlating brain volumes, RNFL, and cognitive functions in MS patients and healthy controls

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**Background:** Brain volume (BV) is a biomarker of neurodegeneration in MS. Retinal nerve fiber layer (RNFL) measured by OCT is another arising biomarker. Both are able to differentiate MS patients from healthy controls (HC) and showed a correlation with physical disability and cognitive impairment. The relationship between RNFL and BV has been generally evaluated in cross-sectional studies, while there are not longitudinal data combining RNFL, BV and cognitive functions (CF) at the same time.

**Aim:** We aimed to assess longitudinally the relationship between RNFL, BV, and CF in MS patients and HC.

**Method:** At baseline (T1) relapsing remitting MS patients and matched HC underwent to 1.5 T brain MRI. SIENAX software estimates the normalized volume of the brain (NBV), grey (NGV), white (NWV) and peripheral grey (pNGV) matter. CF evaluated by BICAMS (including SDMT, CVLT, BVMT), RNFL by Spectral Domain OCT (Heidelberg Engineering), demographic, and clinical data were collected. The eyes with previous clinical or subclinical optic neuritis were excluded. Cognitive reserve (CR) was estimated using a validated tool. The evaluations were repeated after 12 +/- 3 months (T2). Group analyses were performed with T test for unpaired samples. In MS patients, Pearson test analyses the correlation between continuous variables within the 2 groups.

**Results:** We included 54 MS patients (F: 38; mean age: 44 years; disease duration: 11.7 years; mean EDSS: 2.5) and 16 HC (F: 8; mean age: 46 years). At T1 MS patients and HC differ for NBV ( $p=0.003$ ), NWV ( $p=0.001$ ), RNFL ( $p=0.04$ ), SDMT ( $p=0.01$ ). Pearson test showed a correlation between RNFL and CVLT ( $R: 0.366$ ,  $p=0.02$ ), BV ( $R: 0.483$ ,  $p=0.005$ ), NGV ( $R: 0.478$ ,  $p=0.006$ ), pNGV ( $R: 0.494$ ,  $p=0.005$ ), between pNGV and each BICAMS test ( $R: 0.3$ ,  $p=0.01$ ) and between CR and SDMT ( $R: 0.38$ ,  $p=0.003$ ). Longitudinally a significant correlation was found between Delta (T2-T1) RNFL and Delta BICAMS tests ( $R: 0.473$ ,  $p=0.006$ ) Delta RNFL and number of BICAMS altered tests at T2 ( $R: 0.343$ ,  $p=0.04$ ), Delta BV and Delta BICAMS tests ( $R: 0.494$ ,

$p=0.001$ ). No correlation was found in HC between BV, RNFL, and BICAMS tests.

**Conclusions:** Our data support that MRI, OCT and CF could distinguish MS from HC. RNFL, such as BV, is a valid biomarker of neurodegeneration, and contribute to explain the complex interplay determining CF. Our study showed that RNFL, measured with an easy and repeatable instrument as OCT, is useful to longitudinally assess the MS patients.

### Disclosure

The authors have nothing to disclose about this work

### EP1412

#### Brief international cognitive assessment for multiple sclerosis and corpus callosum atrophy index: the correlation between quick and easy-to-use tools in MS patients

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**Background:** Cognitive Impairment (CI) raises concerns since earlier in the course of Multiple Sclerosis (MS) and causes great impact on patients' quality of life. CI correlates with damage of cortical and subcortical cerebral structures. For instance, the atrophy of Corpus Callosum (CC) seems to contribute to cognitive dysfunction in MS. Generally, both CI identification and volumetry of brain structures requires sophisticated techniques that are often inaccessible in clinical practice. The Corpus Callosum Index (CCI) has been suggested as a marker of atrophy and does not require the use of any advanced software. The BICAMS (Brief International Cognitive Assessment for Multiple Sclerosis) is a battery of Neuropsychological Tests (NTs), which includes the SDMT, CVLT-II and BVMT-R, that has been recently proposed as a quick and easy-to-use screening instrument. We have studied the association between these tools, considered ideal for daily clinical practice.

**Objective:** To investigate the correlation between the CC atrophy, evaluated by CCI, and the BICAMS in patients with MS.

**Methods:** Thirty patients with relapsing-remitting MS were included. The BICAMS was applied to these and the CCI were measured in a follow-up routine MRI. The CCI and BICAMS were also estimated in sixty healthy controls. The Correlation Coefficients ( $r$ ) between NTs and CCIs, and their respective effect sizes ( $d$ ), were calculated. All participants signed an Informed Consent Form.

**Results:** There was a significant correlation between SDMT and CCI ( $r = 0.41$ ,  $p < 0.025$ ,  $d = 0.57$ ). BICAMS detected CI in 60% of MS patients with low CCI. When CCI shows no atrophy, 82% of patients present normal NTs.

**Conclusions:** The consistent association between SDMT and CCI points this index as a predictor of information processing speed impairment, oftentimes pattern of CI in MS. The cognitive dysfunctions detected by BICAMS find corresponding damage in brain structures, remarkably the CC atrophy.

### Disclosure

Marco Aurélio Gralha de Caneda: nothing to disclose

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## EP1414

**Treatment optimization using a multidimensional decision model (TIME study): a proof-of concept study to assess a multidimensional standardized documentation model to optimize management of patients with multiple sclerosis in Germany**

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**Objective:** The TIME study aimed at evaluating whether physicians, MS nurses and MS patients will benefit from a novel computer-based management and documentation tool (Multiple Sclerosis Decision Model, MSDM) in terms of optimization of treatment efficiency and uncovering treatment failures.

**Background:** Effective treatment regimens and absence of clinically relevant disease activity are essential goals in today's MS therapy. However, there is no standardized documentation tool to evaluate the complexity of symptoms in MS patients longitudinally. The MSDM has been proposed as an algorithm to detect multimodal clinical changes based on factors such as relapse, disability progression, MRI, cognition, and patient reported outcomes. The feasibility of this tool in everyday practice was investigated including physician, nurse, and patient satisfaction.

**Study design:** This 15-months non-interventional, open-label, multi-center, proof-of-concept study focused on patients with relapsing forms of MS in Germany. The study consisted of a 3-months core and a 12-months extension phase.

**Methods:** MSDM was evaluated on a tablet PC. Acceptance was assessed by physicians, MS nurses and, patients by using specific questionnaires.

**Results:** 110 patients have been recruited in 9 MS outpatient treatment centres. 3-months after the start of the observation, most neurologists (n=6) agreed that the inclusion of neuropsychological factors and the involvement of patients for decision making is highly warranted. However, acceptance rates from neurologists were only moderate, primarily due to demands in time and effort. Acceptance of the tool by MS nurses (n=8) was good. The tool showed high acceptance rates in patients (n=69). Presented numbers so far are preliminary and final data will be presented.

**Conclusion:** A standardized, multidimensional approach to document clinical symptoms longitudinally is warranted to optimize treatment in MS patients. MSDM represents a novel and useful approach covering various relevant disease aspects and supporting disease management.

## Disclosure

MS has received honoraria for scientific lectures or consultancy from Bayer Healthcare, Biogen, Baxalta/Shire, CSL Behring, Euroimmune, Grifols, Merck-Serono, Novartis, Roche, Sanofi-Genzyme, and Teva. His institution received research support from Bayer Healthcare, Biogen Idec, Genzyme, Merck-Serono, Novartis, and Teva.

BK has received honoraria for serving on advisory boards and as speaker from Merck Serono, Biogen-Idec, Sanofi/Genzyme, Teva and Novartis.

RS is a Biogen Employee. IKP has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Adamas Pharma, Almirall, Bayer Pharma, Biogen, Genzyme, Merck Serono, Novartis and Teva. She has received research support from Merck Serono, Novartis, the German MS Society and Teva.

## EP1415

**Epicardial fat tissue in patients with multiple sclerosis**

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**Background and purpose:** The epidemiological studies confirm an increased risk of cardiovascular disease in multiple sclerosis and epicardial adipose tissue (EAT), a type of visceral adipose tissue surrounding the heart and coronary vessels has been implicated in the development of coronary artery disease. We sought to investigate the correlation between **EAT** and the disease - disease severity in multiple sclerosis (MS) patients.

**Methods:** Twenty eight multiple sclerosis (MS) patients (MS duration 8 (4-16) years, aged 41 ± 16 years; female/male: 16/10) and 28 healthy controls both with no known cardiovascular risk factors were enrolled into the study. Disease severity was evaluated by Extended Disability Status Scale (EDSS). The EAT was measured via two-dimensional (2D) M-mode echocardiography.

**Results:** EFT was significantly higher in patients compared to controls (3.6 ± 1.2 mm vs. 3.1 ± 0.7 mm, P < 0.05). We did not observe correlations between the EFT levels and MS duration, relapses, EDSS, optic neuritis, oligoclonal bands (p>0.05).

**Conclusions:** The reason for the increase in EAT in patients with MS is unknown, but it is probably multifactorial, with genetic, immune-mediated inflammatory factors having a role. Thus, along with the increased prevalence of cardiometabolic risk factors and systemic inflammation, EAT can probably be another important contributor to the higher cardiovascular risk observed in MS. These findings deserve to be studied closer in a broader spectrum of comorbidities in MS.

## Disclosure

No conflict of interest

## EP1416

**An improved assay for therapeutic dose monitoring of natalizumab**

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Natalizumab is a highly efficacious treatment option for patients with relapsing-remitting multiple sclerosis (MS), but carries a risk of JC polyomavirus driven progressive multifocal leukoencephalopathy (PML). Recent data has suggested that patients on extended interval dosing schedules have a reduced rate of PML consequent to lower natalizumab exposure. However, there is

significant variation in steady state drug levels in natalizumab patients, suggesting a need for a therapeutic dose monitoring assay that can identify the patients with the highest free trough levels of natalizumab that are candidates for dose extension. We have previously described a specific mimotope peptide for the capture and quantification of free and active natalizumab in serum. The peptide binds to the antigen binding site of natalizumab and competes for binding with the target  $\alpha 4$  chain of integrin as shown by flow cytometry. We compared a mimotope peptide based ELISA assay with an anti-idiotypic based assay using a commercially available anti-natalizumab antibody. Both assays were benchmarked against a cell based assay in which samples were applied to VLA-4 positive cell lines. The peptide based ELISA was consistently closer in value to the cell based assay while the anti-idiotypic assay almost always reported a higher value. While both the peptide and anti-idiotypic cross compete in ELISA and block natalizumab binding in the cell based assay, we hypothesized that the anti-idiotypic antibody could bind to natalizumab that was incapable of binding target. We gently heat denatured natalizumab and observed a loss of binding in the cell based assay that was also observed in the peptide ELISA, whereas the anti-idiotypic reported the full natalizumab concentration regardless of the time of heat treatment. Thus we postulate that there is significant but variable amounts of natalizumab that is no longer able to bind target at the time of trough sampling in treated patients and that the surrogate ligand peptide mimotope ELISA is a more accurate measure of active drug. A second generation peptide was developed by amino acid replacement scanning of the original mimotope. When used in the ELISA assay, this affinity matured peptide had roughly 10 times greater sensitivity, resulting in an assay with an estimated limit of detection of less than 500ng/ml. Full assay validation is ongoing.

## Disclosure

Bradley Messmer: nothing to disclose

## EP1417

### Evaluation of the Human Activity Profile on patients with multiple sclerosis

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**Objective:** To investigate the reliability, validity and responsiveness to change of the Human Activity Profile (HAP), a self-report questionnaire measuring physical activity, in patients with multiple sclerosis (MS).

**Methods:** Group of 25 patients with MS completed the following self-report questionnaires: HAP, Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis Quality of Life-54 (MSQOL54). EDSS disability level was determined and walking speed assessed by 10-Meter Walking test (10MWT).

Responses on the HAP resulted in 2 scores: maximum activity score (MAS) and adjusted activity score (AAS). These scores were statistically correlated with the other tests and examined for test-retest reliability. A subset of patients (12) participated in a 12-week supervised aerobic exercise programme, while others

served as control. Same measures were repeated at end of 12 weeks.

**Results:** Intraclass correlation coefficient (ICC), calculated on control group, was 0,97 for both MAS and AAS. Significant correlations were found between HAP scores and subscale scores from MFIS and MSQOL54, that assess physical functioning, EDSS and 10MWT. After 12 weeks of exercise, a decrease of physical fatigue, as measured by Body subscale of MFIS (MFIS-B), was found, although not statistically significant ( $p=0,054$ ). A statistically significant increase in Energy subscale of MSQOL54 (MSQOL54-E;  $p=0,022$ ) was reported by control group. No significant correlation between MFIS-B and MSQOL54-E was found. In both groups, no statistically significant change was observed in HAP, EDSS and 10MWT. In response to 12 weeks of exercise, the effect sizes for MAS and AAS were 0,2 and 0,04, respectively, similar to that of the MFIS and MSQOL54.

**Conclusion:** The correlations between HAP and physical function subscale scores from MFIS and MSQOL54, EDSS and 10MWT demonstrate that HAP is a valid and, as demonstrated by ICCs, also a reliable measure of physical function in patients with MS. After 12 weeks of exercise, no major change in physical functioning was detected by any of the measures. HAP displays a similar sensitivity to change as the other questionnaires. Along with simplicity of use, HAP could be a valuable assessment tool for patients with MS.

## Disclosure

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## EP1418

### Do color vision testing and OCT parameters reflect the sub-clinical optic nerve involvement in multiple sclerosis?

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**Introduction:** Multiple sclerosis (MS) is an inflammatory demyelinating disease of central nervous system (CNS). Acute idiopathic demyelinating optic neuritis is frequently the initial manifestation. In this study, we aimed to discuss the value of color vision testing to detect possible optic nerve involvement in patients with MS who had no history of optic neuritis.

**Methods:** 28 RRMS patients with 56 eyes and age-sex matched 25 healthy controls with 50 eyes were included to this study. We evaluated color vision with Farnsworth-Munsell 100 hue test and retinal nerve fiber layer thickness (RNFL) was determined by optical coherence tomography (OCT). Pattern visual evoked potentials (PVEP) were also performed. EDSS scores, duration of disease, history of treatment were all recorded.

**Results:** 28 RRMS patients (mean age  $39,68 \pm 9,68$ ) and 25 healthy controls (mean age  $38 \pm 5,94$ ) were included. In patient group, 20 were female (71,4%), 8 were male (28,6%). Control group contained 17 female (68%), 8 male (32%). P100 latencies were significantly delayed in patient group than controls. ( $p < 0.05$ ). In patient group mean RNFL thickness was  $85.79 \pm 13.8 \mu m$  while the



thickness of RNFL was  $89.24 \pm 8.55 \mu\text{m}$  in controls. Mean temporal RNFL thickness was  $57.64 \pm 14.13 \mu\text{m}$  in patients and  $67.64 \pm 11.68 \mu\text{m}$  in controls. Statistically significant thinning was found in temporal quadrant in patient groups than controls ( $p=0.002$ ). There was a negative correlation between the total error scores and RNFL thickness in patient group ( $p=0.016$ ;  $r: -0.320$ ). There were also negative correlations between the red green-blue yellow scores and temporal quadrant thickness in patient group, respectively ( $p=0.006$ ;  $r: -0.363$ ,  $p=0.004$ ;  $r: -0.383$ ).

**Conclusion:** This ongoing study showed that PVEP, OCT parameters, Farnsworth-Munsell 100 hue test were all correlated to detect subclinical optic pathway involvement in multiple sclerosis patients.

### Disclosure

None of the authors identify a conflict of interest. This research did not receive any grant from funding agencies.

## Economic burden

### EP1420

#### Disability and unemployment utilization in patients with multiple sclerosis

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**Background:** Multiple sclerosis (MS) is a disease that affects young adults and can lead to significant disability and unemployment. The aim of this study is to explore the effects of multiple sclerosis on employment across age groups.

**Methods:** This is a cross-sectional retrospective data analysis using a clinical database containing patient data from a single tertiary care MS center after IRB approval. Patients were divided by years since diagnosis:  $< 10$ ,  $10-19$ ,  $20-29$ ,  $\geq 30$ . For each group the percentage of patients on government certified disability and/or unemployed was calculated. The percentage of patients who were on disability, unemployed, and/or retired was also calculated.

**Results:** A total of 854 patients age 18 to 65 with a diagnosis of MS were included in the study

( $F=620$ ,  $M=234$ ). Patients  $< 18$  or  $> 65$  years of age or with no employment data available were excluded. Of these patients 612 (71.6%) carried a diagnosis of relapsing remitting MS (RRMS), 179 (21.0%) carried a diagnosis of secondary progressive MS (SPMS), and 63 (7.4%) carried a diagnosis of primary progressive MS (PPMS). Among all patients 186 (21.8%) patients were on disability and/or unemployed. Furthermore, 267 (31.3%) patients were on disability, unemployed, and/or retired. The percentage of patients who were either unemployed or on disability was higher among patients who were at least

10 years from diagnosis (33.8% vs. 23.1%). Age at diagnosis was not associated with disability and/or unemployment status ( $p=0.822$ ). The percentage of patients on disability, unemployed, and/or retired increased with number of years since diagnosis and included 28.4% of patients with  $< 10$  years since diagnosis and 77.8% of patients with  $\geq 30$  years since diagnosis. Patients w/

PPMS were more likely to be disabled, unemployed, and/or retired ( $p < 0.001$ ). Male and female patients were equally likely to be unemployed and/or on disability.

**Conclusion:** The percentage of patients who are on disability or are unemployed is higher in patients who have carried a diagnosis of MS for at least 10 years. PPMS patients were the more likely to be unemployed when compared to patients with either RRMS or SPMS. Furthermore, neither age at diagnosis nor patient sex was associated with employment status.

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Syed Rizvi: nothing to disclose

### EP1421

#### Satisfaction analysis of nursing care delivered to patients with multiple sclerosis using virtual technology in British Columbia, Canada

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Fraser Health Multiple Sclerosis Clinic, Burnaby, BC, Canada

**Background:** The Fraser Health Authority (FHA) is the largest and fastest growing health region in British Columbia (BC), serving a population base of 1.46 million in an area of approximately 10,000 square kilometres. Travel time from east to west borders is 2 hours. The Fraser Health Multiple Sclerosis (FHMS) Clinic was established August 2004 in Burnaby BC to serve more than 3000 persons living with multiple sclerosis (MS). The large geographical area, coupled with the limited specialized resources creates physical, financial and/or geographical accessibility barriers. To address this issue, in April 2015, the FHMS Clinic opened a Satellite Clinic in Abbotsford Regional Hospital, located more centrally in the area. To maintain a high level of specialty care, a nurse clinician and MS neurologist travelled to the clinic weekly. However, travel time and cost to the satellite clinic and the inability to attend to the nursing duties in the Burnaby clinic were significant factors that lead to the development of a unique tele health model of nursing care. The Virtual Nursing Program (VNP) commenced in June 2016, and continues to function with a rotation of MS neurologists, who see the patients in Abbotsford, and an assistant, to connect the patient through Skype for Business (S4B) with the nurses who are situated in the clinic in Burnaby. Nurses replicate educating, counselling, monitoring and managing MS symptoms through technology. The physician can communicate with the nurses via S4B to discuss each patient and the care plan, as they do in the Burnaby site. Additionally, education materials are handed to the patients, by the assistant, as directed by the nurses. **GOAL:** To determine if MS patients, MS neurologists and MS nurses participating in the VNP are satisfied with this mode of care.

**Method:** A satisfaction survey using a 5-point Likert scale was given to 59 MS patients, 3 neurologists and 2 nurses.

**Results:** Results of the survey were analyzed for level of participant satisfaction, recommendations, and verbal feedback of experience. A majority of the patients scored very satisfied, with overall scores improving as the clinic gained experience in this

mode of care delivery. Few patients noted preference for face to face interaction. Neurologists and nurses scored similarly.

**Conclusion:** Satisfaction with the virtual nursing program confirmed the viability of providing specialized care to patients in poorly accessible areas of the health region.

### Disclosure

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Jill Nelson, RN, BScN, MSCN: I have received honorariums for participation in nursing advisory boards from the following Pharmaceutical companies: Novartis Pharmaceuticals Canada Inc., EMD Serono, Genzyme Canada, Teva Canada Innovation, Biogen Canada Inc., Roche Canada

### EP1422

#### Multiple sclerosis treatment decisions: EDSS independent disease impact/reserve and the use of additional economically impactful milestones that matter

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<sup>5</sup>Neuropsychology Associates, Fairfax, VA, <sup>6</sup>Dept of Neurology and Washington Neuropsychology Research Group, Georgetown University Hospital, Washington, DC, United States, <sup>7</sup>NeuroTrax Corporation, Modiin, Israel

**Objective:** Explore objective computerized cognitive outcome measures to identify MS disability trajectory as it relates to impact not always apparent by relapse, EDSS or MRI.

**Background/rationale:** MS, characterized by relapses/progression, is traditionally measured by EDSS/MRI change and relapse rate reduction. EDSS change is primarily driven by walking impairment but this does not account for cognitive impact/reserve nor accumulation of cognitive impairment. Cognitive impairment impacts abilities not addressed by traditional metrics (e.g. employment, ability to drive, and fall risk for simple or complex daily activities). There are multiple available disease modifying therapies (DMT) of varied routes/potencies making individual treatment choice/change problematic. A patient centric objective analysis of likely trajectory of economically important milestones relating to predictive loss of such abilities an alternative approach to guiding treatment choice/change. This objective/quantitative, EDSS independent, approach of likely disability trajectory might improve decision making regarding DMT choice/change and offer a path to compare outcome measures across clinical trials.

**Methods:** Retrospective cross-sectional review of a prospective digital MS registry obtained in the course of routine care utilizing standardized computerized cognitive testing to evaluate the

relationship of cognitive impairment (number of cognitive domains impaired (CDI) >1 standard deviation from age/education normal) on patient reported outcome disability (unemployment, loss of driving, increased fall risk) in people with EDSS < 7.

**Results:** Increasing accumulated number of CDI is associated with progressive loss of: employment (N=543, CDI-0=63%, CDI-1=53%, CDI-2=45%, CDI-3=23%) driving (N=126, CDI-0=86, CDI-1=69%, CDI-2=61%, CDI-3=20%) and reduced safety with increased fear of falling for simple daily activities [(FOF-SDA), N=174, CDI-0=74%, CDI-1=69%, CDI-2=35%, CDI-3=29%) and increased fall of falling for complex daily activities [(FOF-CDA), N=174, CDI-0=71%, CDI-1=65%, CDI-2=33%, CDI-3=32%).

**Conclusions:** Tracking disease impact by economically important milestones trajectory beyond EDSS/MRI or relapse can be obtained by use of cognitive testing to provide patient centric information predicting loss likelihood of important milestones not completely dependent upon EDSS which might provide a pathway of actionable change to monitor therapy choice or disease progression.

### Disclosure

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Doniger G: employee of NeuroTrax

### EP1423

#### Dutch trial-based economic evaluation of an intensive social-cognitive treatment (Can Do Treatment) in patients with relapsing remitting multiple sclerosis and low disability

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**Objective:** To evaluate the cost-effectiveness of the Can Do Treatment (CDT) which aims to improve self-efficacy and establish autonomy in patients with relapsing remitting multiple sclerosis (RRMS) and low disability.

**Treatment:** The CDT, an intensive social cognitive program contains various sessions provided in one weekend to patients and partners by a multidisciplinary team aiming to identify and reduce "stressors" which they experience due to RRMS in their daily life.

**Methods:** The economic evaluation from a societal perspective with a follow up of 6 months was performed alongside a randomized controlled trial evaluating two groups; CDT patients (CDT) and care as usual patients who had the option to receive CDT after the controlled study phase (control). Included costs were medical costs (inpatient and outpatient), cost of productivity losses, informal care and travel costs. The incremental cost effectiveness ratio (ICER) is expressed in cost on the Multiple Sclerosis Self-Efficacy Scale-Control (MSESS control) and the incremental cost utility ratio (ICUR) in the cost per Quality Adjusted Life Years (QALY). Bootstrap analyses and sensitivity analyses were performed to determine the robustness of the findings. The costs of (un)prescribed drugs, aids and tools were not taken into account in the current analyses. The final results, including these previously mentioned cost categories will be available for the presentation at the congress.

**Results:** The two groups of 79 patients showed comparable baseline characteristics. Results from the preliminary analyses suggest that the average total cost difference was not significantly different between the two groups; that the ICER shows higher costs and more effects in the CDT group; and that the ICUR shows higher costs and lower effects for the CDT group. The bootstrap and sensitivity analyses confirm the preliminary base case findings.

**Conclusions:** These preliminary results of the economic evaluation suggest no cost effectiveness of the CDT. A reduction of intervention costs could improve change of the CDT being cost effective.

## Disclosure

This study is funded by the National MS foundation, The Netherlands, Rotterdam and The Netherlands.

## EP1424

### Health needs, utilization and cost coverage in MS: a NARCOMS, NMSS, iConquerMS survey

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**Background:** Health care services needed for management and treatment of MS are not always covered by health insurance (HI). Even with HI coverage, out of pocket costs are often incurred, resulting in emotional, physical, or financial stress.

**Objective:** Assess need for services, utilization when needed, and insurance coverage and costs in persons with MS in the prior 12 months.

**Methods:** Persons diagnosed with MS, US residents, ages 18-65, were surveyed in Fall 2016 through the National MS Society, the North American Research Committee on MS (NARCOMS), iConquerMS, and regarding healthcare services needed, used, and covered by HI in the prior 12 months. Services included medical professionals (MP: primary care, neurologists, nurse practitioners), behavioral health (BH), rehabilitation (Rehab), integrative/complementary medicine (ICM), medical equipment (MEQ), Laboratory (Lab) or imaging (IMG) services, prescriptions (Pres), inpatient care (INP), short-term/home-care nursing or rehabilitation (STC),

emergency room (ER), and preventative medicine/wellness (PrevM). Results are presented as percent (%), Mean(SD), or Median(IQR).

**Results:** Of the 2507 respondents that met the general eligibility criteria, 2323 (92.7%) completed information regarding age, gender, duration of MS, had HI and needed at least one healthcare service: 53.6(8.4) years old, 3.4% Hispanic/Latino, 91.8% Caucasian, 3.2% African American, 82.8% female, with a mean disease duration 16.5(8.4) years, 67.0% Relapsing MS, 20.5% SPMS, 5.6% PPMS. The median(IQR) services needed was 6(4, 7), used 5(4, 6), and covered by HI 4(4, 6). Over 90% of respondents indicated they needed MP (97.5%), 95.0 Pres, 92.1 each Lab or IMG; with less than 40% needing all other services 38.9 Rehab, 36.6 PrevM, 32.4 ICM, 28.6 MEQ, 22.6 BH, 21.5 ER, 13.5 INP, 4.6 STC. More than 80% of services needed were used, excepting 73.1 IMG. Of services used, more than 85% were covered by HI, excepting 61.3 MEQ, 42.1 PrevM, 41.5 ICM.

**Conclusions:** As expected standard healthcare services such as practitioner visits, lab and imaging were the most needed services, though imaging was the least used of needed services. And while most used services were covered by HI, nontraditional services such as medical equipment, integrative or complementary medicine, and preventative medicine and wellness were least likely to be covered by insurance.

## Disclosure

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## EP1425

### Relapse resolution and HCRU in patients with multiple sclerosis: a retrospective study of relapse therapy alternatives to corticosteroids

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**Background:** Corticosteroids (CS) are the mainstay treatment of relapses in patients with multiple sclerosis (MS); other agents include repository corticotropin injection (RCI; H.P. Acthar® Gel), intravenous immunoglobulin (IVIG), or plasmapheresis (PMP). Our study evaluated patients with MS relapse, healthcare resource use (HCRU), and effectiveness of CS alternatives in relapse resolution using the Humana Research Database. Humana policy considers CS to be first-line relapse therapy.



**Methods:** Humana's Commercial and Medicare Advantage claims data from 1/1/08-7/31/15 were utilized. An MS relapse was defined as an inpatient stay (IP) with a principal diagnosis of MS (ICD-9-CM 340.xx) or an outpatient visit [OP, including emergency department (ED)] with a MS diagnosis, and a medical or pharmacy claim for second-line treatment (RCI, IVIG, PMP) within 30 days. The first relapse event and treatment were considered the index event and treatment. Relapse events were considered unresolved if >1 relapse occurred within 30 days. In RCI and PMP/IVIG groups, relapse events and HCRU (IP, OP, ED, total visits) were evaluated during 1-year follow-up (1 year); relapse events were also evaluated during 2-year follow-up (2 years). Comparative analyses were conducted, using chi-square tests for categorical variables and t-tests for continuous variables.

**Results:** PMP and IVIG were combined into 1 group, due to sample size. At 1 year, 232 RCI and 141 PMP/IVIG patients were identified with mean (SD) unresolved relapse events of 0.6 (2.0) and 5.3 (7.1), respectively. 81.5% of patients receiving RCI had no unresolved relapses vs. 36.2% receiving PMP/IVIG. Patients receiving RCI had lower all-cause HCRU, except ED (mean differences): total visits (12.9), IP (0.2), ED (0.0), and OP (12.7). At 2 years, 155 RCI and 104 PMP/IVIG patients were identified with mean (SD) unresolved relapses of 1.2 (3.5) and 8.0 (11.6), respectively. 73.5% of patients receiving RCI had no unresolved relapses vs. 33.7% receiving PMP/IVIG. All results, except for ED visits, were significant at  $p < 0.02$ .

**Conclusions:** At 1 year, patients receiving RCI had significantly lower unresolved relapses and lower mean total, IP, and OP visits; superior resolution with RCI continued at 2 years. Results suggest RCI should be considered for relapse treatment prior to PMP/IVIG in appropriate patients. Limitations of claims data apply; index events were first observed and not incident.

## Disclosure

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Richard Sheer: A shareholder of Humana Inc. and an employee of Comprehensive Health Insights, Inc., a wholly-owned subsidiary of Humana Inc.

Phil Schwab: A shareholder of Humana Inc. and an employee of Comprehensive Health Insights, Inc., a wholly-owned subsidiary of Humana Inc.

Tara Nazareth: An employee and stock holder of Mallinckrodt Pharmaceuticals, Inc.

Tzy-Chyi Yu: An employee and stock holder of Mallinckrodt Pharmaceuticals, Inc.

## EP1426

### Access Barriers to disease-modifying therapies in Latin America: the impact of who makes treatment decisions and when and why this is done

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**Introduction:** Multiple Sclerosis (MS) patients who are prescribed disease-modifying therapies

(DMTs) may lack access to their medication for reasons such as interchangeability from providers, copayment costs, pharmacy requirements, provider requirements, insurance coverage changes and restrictions. The consequences are associated with poorer adherence and increased risk. There is a need in Latin America to understand MS patients' perspectives on access barriers to DMT medication.

**Objectives:** To describe and to analyze problems for accessing DMTs in Latin America.

**Methods:** Responses were obtained from nine countries (Argentina, Bolivia Brazil, Chile, Colombia, Mexico, Peru, Uruguay and Venezuela) regarding four main questions: 1) How do patients resolve their DMT access issues? 2) What are the clinical and ethical consequences of DMT access barriers? 3) Who is involved in helping patients access their DMTs? 4) What percentage of patients access their DMTs?

**Results:** 6/9 countries: neurologist non-expert confirms diagnosis and decides treatment. Time diagnosis-treatment: 7/9 countries 4-6 months; 2/9 time was longer (8-12 months). Between 90 and 100% of patients access their DMTs in 7/9 countries; however, in 3/9 countries the Social Security decides what treatment patients need, according to the cost. This means that many choices are made between innovative and -generic drugs differing from what the neurologist prescribed, which impacts on clinical and ethical issues. Some of the countries have more than three generic version available for some innovative drugs. We discuss the ethical issues at the time of decision-making regarding treatment.

**Conclusion:** Every country represented in this Latin American forum needs to understand who is responsible for managing the risks of a given treatment. One of the most important aspects of this new era of generics, biosimilars and follow-on drugs is not only the cost but also what place the expert has in making decisions on treatments.

## Disclosure

A. Carra; Y. Fragoso; MA. Macias-Islas; J. Steinberg; C. Carcamo Rodriguez; JC Duran Quiroz; Alessandro Finkelsztein; J. Garcia Bonitto; R. Leon Aponte; G. Orozco; C. Oehninger Gatti; A. Tarulla; D. Vizcarra Esobar; C. Vrech: nothing to disclose

## EP1427

**Activities of daily living, work productivity, and reliance on caregiver in patients with primary progressive multiple sclerosis**N. Wu<sup>1</sup>, N. Thomas<sup>1</sup>, E. Ma<sup>1</sup>, W.-S. Yeh<sup>1</sup>, E. Jones<sup>2</sup><sup>1</sup>Genentech Inc, South San Francisco, CA, United States,<sup>2</sup>Adelphi Real World, Manchester, United Kingdom

**Background:** Primary progressive multiple sclerosis (PPMS) is characterized by steadily increasing neurologic disability from disease onset, with or without temporary plateaus in disease progression. PPMS is a chronic disease that primarily affects patients of working age; however, there is a lack of data on the impact PPMS has on patients' work productivity and ability to live independently.

**Goals:** To compare the ability to perform daily self-care activities, work productivity, and reliance on caregiver between patients who have PPMS and patients who have relapsing remitting MS (RRMS).

**Methods:** This study used data from the patient record form (PRF) of the Adelphi Multiple Sclerosis Disease Specific Programme, a cross-sectional study collecting data from 487 neurologists and 5402 patients in the France, Germany, Italy, Spain, United Kingdom, and United States between November 2015 and March 2016. A total of 916 PPMS and 3,472 RRMS patients were included. Self-care activities were assessed by activities of daily living (ADL) and instrumental activities of daily living (IADL). Productivity and independency were examined by whether a patient was able to work full time and whether he/she had a caregiver, respectively. Adjusted analyses were performed to control for potential confounders.

**Results:** PPMS patients were older (51.2 vs. 38.1,  $p < 0.001$ ), more likely to be males (54.8% vs. 31.8%,  $p < 0.001$ ), had a longer disease duration (7.0 vs. 4.6 years,  $p < 0.001$ ), had a higher Expanded Disability Status Scale (EDSS) score (4.9 vs. 2.1,  $p < 0.001$ ), and were less likely to be on a current treatment with a DMT (36.7% vs. 83.4%,  $p < 0.001$ ) than RRMS patients. Compared to RRMS, a higher proportion of PPMS patients needed assist on at least one ADL (45.0% vs. 6.4%,  $p < 0.001$ ) and IADL (62.2% vs. 15.2%,  $p < 0.001$ ). In addition, PPMS patients were less likely to work full time than RRMS patients (18.8% vs. 52.3%,  $p < 0.001$ ). Finally, a higher reliance on professional caregiver (18.2% vs. 1.4%,  $p < 0.001$ ) and family caregiver (53.7% vs. 16.7%,  $p < 0.001$ ) was observed in PPMS than in RRMS.

In adjusted analyses, all of the above findings were consistent after controlling for confounders.

**Conclusions:** Compared with RRMS patients, PPMS patients had a significantly higher burden on their ability to perform self-care activities, work full time, and live independently. These findings highlight the high unmet need in PPMS for an effective DMT.

**Disclosure**

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N. Wu is an employee of Genentech, Inc.

N. Thomas is an employee and shareholder of Genentech, Inc.

E. Ma is an employee and shareholder of Genentech, Inc.

W-S Yeh is an employee and shareholder of Genentech, Inc.

E. Jones has no conflict of interest and is a paid employee of Adelphi Real World

## EP1428

**Cost analysis of a relapse-free patient in relapsing-remitting multiple sclerosis**L. Romero-Pinel<sup>1</sup>, E. Matas<sup>1</sup>, L. Bau<sup>1</sup>, R. Juvany<sup>2</sup>, V. Casado<sup>3</sup>, M. Huerta<sup>4</sup>, A. Martínez-Yélamos<sup>1</sup>, S. Martínez-Yélamos<sup>1</sup><sup>1</sup>Department of Neurology, Multiple Sclerosis Unit (EMxarxa),<sup>2</sup>Pharmacy Department, Hospital Universitari de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, <sup>3</sup>Department of Neurology,Hospital de Mataró, <sup>4</sup>Department of Neurology, Hospital de

Viladecans, Barcelona, Spain

**Background:** Nowadays efficacy and safety of disease-modifying therapies (DMTs) in multiple sclerosis (MS) are well known but it lacks data to evaluate its cost-effectiveness. This knowledge would be useful to improve clinical management and to establish risk-sharing schemes of payment in health systems.

**Objective:** To analyze the cost per year of a relapse-free patient in a cohort of relapsing remitting multiple sclerosis (RRMS) treated with first or second-line DMTs.

**Patients and methods:** Patients diagnosed with MS, followed in our MS unit and belonging to our health district in 2016 were evaluated. Our health district comprised 201192 inhabitants by 2016 and our center has the only MS unit. From them, patients diagnosed with RRMS were retrospectively selected for this study. Clinical and radiological data was collected prospectively using the European Database for Multiple Sclerosis (EDMUS) on a 6-monthly basis and at the time of relapse. Patients were classified in two groups, treated and not treated with DMTs during 2016 and in another two groups according to the presence or absence of at least one relapse during the same year. The mean cost of DMTs during 2016 of all RRMS patients was analyzed as well as the cost of a relapse-free patient.

**Results:** 181 patients from our health district were diagnosed with MS and followed in our MS unit, resulting in an MS prevalence of 90 per 100000 inhabitants. This rate was representative of the expected prevalence of MS in epidemiological population-based studies performed in our area. 158 patients diagnosed with RRMS were selected for our study. They were 71% women, their mean age at onset was 30.6 years, their mean disease duration was 16.3 years, and their median irreversible EDSS was 2.0. From them, 101 patients (63.9% of the cohort, 95% CI: 56.2-71.0%) were treated with DMTs during 2016. 120 patients (75.9% of the cohort, 95% CI 68.7-81.9%) remained free of relapses during 2016. The mean cost of DMTs per patient in 2016 was 7414.3 euros (95% CI: 6325.2-8503.4) when we considered all RRMS patients. The cost per year of DMTs of a relapse-free patient was 9762.2 euros.

**Conclusion:** The cost per year of a relapse-free patient may be a good health indicator to evaluate cost-effectiveness in RRMS patients treated with DMTs and to compare one population to another.

**Disclosure**

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## Neuro-ophthalmology

### EP1429

#### Is retinal oximetry useful in diagnosis of neuromyelitis optica Devic?

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**Purpose:** An assessment of retinal oxygen saturation in the optic nerve in patients with demyelinating disease and comparison the difference between clinically isolated syndrome (CIS), relapse remitting multiple sclerosis (RRMS) and neuromyelitis optica Devic (NMO).

**Methods:** There were investigated 46 patients with MS (29 with CIS, 17 with RRMS) and 5 with diagnose of NMO. All patients were examined by using optical coherence tomography (OCT Spectralis, Heidelberg Engineering, Germany), automatic optical oximetry (Oxymap, ehf. Reykjavik, Iceland), and by using visual evoked potentials (Metronic Keypoint®, Minneapolis, USA).

**Results:** Arterial and venous saturation and arterio-venous difference (AVD) were reported. The results were compared among the three groups. There were found out changes in the saturation, especially in patients with acute relapse of ON. The most significant changes of AVD were observed in group of NMO.

**Conclusion:** Assessment of retinal oxygen saturation could be used as another diagnostic method in suspicion from NMO. There is an assume that oximetry could reflects changes in acute phase of ON. The higher metabolic demand cause bigger oxygen consumption and higher AVD, while degenerative process cause lower AVD. There will be needed more patients to confirm the fact.

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### Disclosure

none

### EP1430

#### Vogt-Koyanagi-Harada disease is an important differential diagnosis for autoimmune acute visual impairment

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**Introduction:** Vogt-Koyanagi-Harada (VKH) disease is a systemic illness of autoimmune origin in which T cells target melanocytes in individuals susceptible to the disease. Clinical manifestations typically include signs and symptoms relating to the eye, ear, skin and central nervous system (CNS). Acute visual manifestations of VKH include acute uveitis with bullous serous retinal detachment and optic disk hyperemia. Previous ocular penetrating trauma, eye surgery and any other ocular disease that could be confounded with VKH must be ruled out for correct diagnosis and treatment of the condition. Among these differential diagnoses are other autoimmune diseases potentially leading to visual loss, such as multiple sclerosis (MS) and neuromyelitis optica (NMO). The objective of the present study was to report on a series of 22 well-documented VKH cases from Brazil.

**Methods:** Detailed reports on patients diagnosed with VKH were reviewed by neurologists and ophthalmologists caring for these individuals. Data are presented descriptively.

**Results:** There was clear predominance of females (91%), and the median age at the initial manifestation of VKH was 34 years. All patients had severe visual manifestations of the disease and 68% of them had concomitant neurological signs and symptoms (headache, ataxia, vertigo, dysphagia, motor deficits and neuropsychiatric manifestations). Despite prompt diagnosis and treatment in all cases, three patients presented new episodes of uveitis, five patients evolved with cataracts and one with glaucoma, and two patients were left with severe permanent loss of vision. Seven patients had been referred to the neurologist with the diagnosis of "optical neuritis" by the first physician attending the case. Other diagnoses for referral to neurologists were viral meningitis, vertigo, Behcet's disease, MS and NMO.

**Conclusion:** Like MS and NMO, VKH is a cause of acute visual impairment mainly affecting young women. Awareness of VKH disease is of essence in neuroimmunology.



## Disclosure

Yara Dadalti Fragoso, Tarso Adoni, Ellen Yukie F. Chiovatto, Sidney Gomes, Marcus Vinicius M. Goncalves, Myung Kim, Ernane Pires Maciel, Andre Muniz, Roberto Ivo Pasquarelli Neto, Marina A. Camargo Pereira, Luciano M. Simao, Marlos Aureliano D. de Sousa and Nise Alessandra C. Sousa have no conflicts of interest to declare. This study was carried out without any financial support.

## EP1431

### North American Susac syndrome collaboration classification criteria: labels for a broader spectrum of Susac syndrome

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**Background:** Recently proposed diagnostic criteria Susac syndrome (SuS) may not serve patients who have early or atypical SuS. A classification criteria will enable identification and facilitate research for those patients.

**Objective:** To propose classification criteria and rules for classification for SuS that recognize heterogeneity in limited forms of disease.

**Methodology:** Using reported manifestations of SuS, criteria for demonstrating Eye, Ear and Brain involvement were developed. Corpus callosum (CC) lesions were used as an independent biomarker. Classification Rules include all combinations of the presence/absence of CC lesions and the classic triad.

**Results:** Eye involvement can be demonstrated by:

- 1) Branch/Central Retinal Artery Occlusion (BRAO),
- 2) arterial wall hyperfluorescence on fluorescein angiogram,
- 3) history of purported past BRAO, without current FA evidence of diminished dye flow through any vessels but with residual scotoma (documented by visual field testing) and OCT evidence of past BRAO, or
- 4) chronic changes in the retinal periphery that are consistent with residual damage from past Susac retinal vasculopathy (such as capillary dropout, peripheral non-perfusion, neovascularization) and are best explained by SuS.

Brain Involvement can be demonstrated by diffuse encephalopathy and/or a neuropsychiatric syndrome such as psychosis, paranoia, personality change, or amnesia. Ear involvement can be demonstrated with subacute/acute onset of unilateral or bilateral low frequency sensorineural hearing loss, documented by audiogram. Classical CC lesions include typical "snowball" lesions (of various sizes and shapes), "spoke" lesions, "icicle" lesions, and corpus callosum "holes" that are located in the central portion of the CC. The number of lesions may vary from many to a single (but definite) lesion. Classification rules recognize all possible combinations of the above findings and with a total of 11 categories, including definite/probable/possible/isolated feature and classical/atypical depending on presence of CC lesions.

**Conclusion:** The proposed NASSC Classification Criteria use established manifestations of SuS including the presence/absence of the complete triad and CC lesions to provide labels for early SuS who do not meet published diagnostic criteria.

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Robert Rennebohm: Nothing to disclose

## EP1432

### Long-term outcomes in MOG-IgG+ Optic Neuritis

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**Introduction:** The association between Optic Neuritis (ON) and autoantibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) have been reported by several groups but there are still not definite recommendations about long-term treatments to prevent recurrences. In this study, we evaluated the clinical characteristics and the long-term recurrence of our MOG-IgG positive ON cases.

**Methods and results:** We included all patients who presented with isolated ON between December 2014 and December 2015 in a tertiary center in South Brazil. We excluded patients diagnosed with Neuromyelitis Optica Spectrum Disorders (NMOSD) and Multiple Sclerosis (MS). We included 6 ON cases who were MOG-IgG+ and negative to aquaporin-4-IgG using in-house live cell-based assays. They were mainly male (4 males and 2 females), with a mean age of 47 years and all patients, except one, presented bilateral and/or recurrent ON. The brain MRI of all MOG-IgG+ patients was normal or had unspecific white matter T2 lesions. Five patients were followed for a median of 53 (range 43-120) months, but one patient did not return for follow-up visits. Three patients did not present any other attack. Two patients had recurrent ON attacks during follow-up. Three patients received azathioprine. One patient with recurrent ON had persistent MOG-IgG+ at the last visit.

**Discussion:** Previous studies found higher frequencies of recurrent ON in MOG-IgG+ patients, but we observed recurrence in only two MOG-IgG+ patients in a cohort with a first ON attack. Although based on a small sample, our results suggest a significant portion of patients with a single attack, indicating a benign course when comparing to NMOSD and MS.

**Conclusion:** The MOG-IgG+ ON apparently have a benign course with low number of relapses, but the use of long-term immunosuppression may be considered in relapsing and severe cases with persistent MOG-IgG+.

## Disclosure

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Mr. Sommer has nothing to disclose.  
Dr Passos had temporary internship position at Novartis.  
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#### EP1433

##### The use of visual evoked potentials to differentiate optic neuropathies

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**Introduction:** Visual evoked potentials (VEPs) have long been used to investigate patients with optic neuropathies. They complement the structural information given by magnetic resonance imaging and clinical assessment of visual acuity by detecting functional loss in the visual pathway. The analysis of VEPs amplitudes and latencies may aid in the differential diagnosis.

**Methods:** 115 patients admitted in our hospital with suspected optic neuropathy were selected. According to current diagnosis criteria, 4 etiological groups were defined: Multiple sclerosis (MS) (N=36), Neuromyelitis optica (NMO) (N=8), Idiopathic (N= 57), Ischemic (N=9). We analysed VEPs performed in the acute phase and compared these results according to the final diagnosis.

**Results:** 110 patients and 220 eyes were selected. Fourteen patients had bilateral symptoms (N=2 MS, N=9 Idiopathic, N=3 NMO). The VEP analysis showed visual pathway abnormalities in sixty-nine eyes, and none of these were asymptomatic. Mean P100 latency differed among groups ( $p=0.0023$ ), with those diagnosed with MS and NMO showing prolonged latencies, respectively 139 (IQR=30,5) and 126. Analysis of P100 amplitudes did not show significant differences ( $p=0.0852$ ). NMO and ischemic optic neuropathies were associated with a greater proportion of absence visual evoked responses: 50% and 37.5%, respectively, compared with 16.0% in MS ( $p=0.013$ ).

**Conclusion:** Recently a new role for VEPs in MS has been suggested. They are advocated as possible diagnosis and prognostic biomarkers. Nevertheless, their value extends beyond MS and they may help differentiating this entity and NMO or ischemic neuropathies. Our study further confirms previous reports of utility of VEPs in differentiating the etiology of optic neuropathies with different profiles.

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### Comorbidity

#### EP1434

##### Mood disorders and multiple sclerosis: a study based upon the French national health insurance databases

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**Background:** Mental comorbidities are considered as common among patients with multiple sclerosis (MS). They may have impact on care consumption, delay to diagnosis, disability progression, adherence to disease-modifying therapy but also on quality of life. International literature shows that the frequency of mental comorbidity in MS patients is higher than in general population. However, few data are available in France. In this context, the present study was performed to assess the frequency of patients affected by MS having mental comorbidity and more precisely mood disorders.

**Method:** MS Patients were identified between 2011 and 2015 in a random sample issued of French national health insurance system if they meet at least one out of the three following criteria: being under MS long disease duration status, being prescribed at least one disease-modifying therapy (DMT) specific for MS (dimethyl fumarate, beta interferon, fingolimod, glatiramer acetate, natalizumab or teriflunomide), having at least one hospital admission with a MS diagnosis. Mood disorders were considered as present if at least one reimbursement of a specific list of treatments was identified in 2015.

**Results:** A total of 1,153 patients with MS were alive in 2015. Most of them were declared as LDD status (N=1,009) from a median duration of 10 years, female to male sex-ratio was 2.5 and their median age was 50 years. At least one reimbursement for mood disorders treatment was observed for 349/1153 (30.3%) of patients. Of them, 187 received only a treatment specific to depression and 25 only a treatment specific to bipolar disorders. Patients with mood disorders were older than patients without mood disorders (median age: 54 vs 49, respectively) and their number of general practitioner visits was higher (median at 7 visits per year vs 5).

**Conclusion:** This study performed on sample of national health-care databases available in France shows that about one third of patients affected by MS had a prescription for treatment of mood disorders over 1 year period. The next objectives are to extent this analysis on a healthy control group from the French general population in order to compare the frequencies of mental comorbidities but also with control group from the population of people diagnosed with rheumatoid arthritis to estimate the burden of MS on mental health compared to another chronic disease.

#### Disclosure

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#### EP1435

##### Frequency of sleep abnormalities in a Brazilian cohort of patients with neuromyelitis optica spectrum disorder

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**Background:** Among patients with neuromyelitis optica spectrum disorder (NMOSD), sleep abnormalities, fatigue and mood disorders are common comorbidities that can impair quality of life if they are not correctly identified.

**Goals:** To evaluate the frequency of sleep disorders, fatigue and depression in a Brazilian cohort of patients with NMOSD.

**Methods:** Between September 2014 and December 2016, 66 patients with NMOSD were interviewed, in a cross-sectional study. Sleep disorders, fatigue and depression were evaluated through specific questionnaires: Pittsburgh index for sleep quality, restless legs syndrome severity scale, fatigue severity scale, Beck's depression inventory, Epworth scale, and Berlin questionnaire. Unpaired t test or Mann-Whitney test were used for comparing NMOIgG positive and negative patients. A logistic regression model was built to investigate factors associated to the quality of sleep.

**Results:** Mean age of disease onset was 33,85 ( $\pm 13,5$ ), with median disease duration of 9,03 ( $\pm 5,5$ ) years; 50% were Afro-descendants with a 4:1 female:male rate. A complete NMO syndrome (with 2 of the core symptoms: optic neuritis, longitudinal extensive transverse myelitis and/or area postrema syndrome) were observed in 77% of the patients. Only 18 (27%) patients presented a good sleep quality; 35% had excessive daytime sleepiness; 30% were at high risk for presenting obstructive sleep apnea syndrome; 15% had moderate to severe restless legs syndrome; 62% had depression, and 33% had moderate to severe fatigue. When NMOIgG positive patients ( $n = 32$ ) and negative ( $n = 30$ ) were compared, no difference was observed between the two groups. The regression model showed only age was significantly associated with poor quality of sleep (coef 0.84,  $p = 0.03$ ).

**Conclusion:** Sleep disorders and depression are frequent among patients with NMOSD, regardless their NMOIgG status. Older patients seem to have a poor quality of sleep.

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Bichuetti DB has received speaking/consulting honoraria from Bayer Health Care, Biogen Idec, Merck Serono, Genzyme-Sanofi and TEVA and had travel expenses to scientific meetings sponsored by Bayer Health Care, Merck Serono, TEVA and Roche.

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## EP1436

### Assessing the risk of cervical dysplasia in women with MS compared to women without disease using a data linkage approach

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**Background and aims:** The risk of persistent Human Papillomavirus (HPV) infection, cervical dysplasia and HPV-related cancers is unknown in women with multiple sclerosis (MS). Given the long-term and serial exposure of patients to immunomodulatory and immunosuppressive treatments, it is important to determine the prevalence of cervical dysplasia in the MS population compared to other women. Understanding this risk may help guide vaccination guidelines for the highly effective HPV vaccine in this population.

**Methods:** We identified all women aged 18 to 70 with a primary diagnosis coded at hospital separation as MS through the Victorian Admitted Episode Database. The cervical screening history of this cohort was identified using probabilistic data linkage to women who had at least one cervical screening episode between 2009 - 2013 recorded on the Victorian Cervical Cytology Registry. Cervical dysplasia outcomes identified were: cytological low- and high-grade abnormalities (LGA, HGA) and histologically confirmed abnormalities (HisA). Results were stratified by age and intergroup comparisons were performed.

**Results:** A cohort of 2382 patients with MS was identified, and compared with 929,670 women in the general population. Overall, the results show a similar proportion of cytological and histological abnormalities between the MS cohort and the general population. In the MS cohort, 7.18% had LGA, 2.35% had HGA, and 1.68% had HisA; these rates were 6.84%, 2.46% and 2.31%, respectively, in the general population. In the younger age groups (25-34 years), the MS cohort had higher rates of all abnormalities, but these rates dropped below that of the general population in the later age groups (60-69 years).

**Conclusion:** The data demonstrates similar rates of cervical dysplasia for women with MS and the general Victorian population. While the results are reassuring, the lack of data on DMT-exposure makes it difficult to assess risk on an individual basis. Physicians should remain vigilant and recommend screening and vaccination to all patients with multiple sclerosis.

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## EP1437

**A prospective study of fracture risk, fall risk and serum vitamin D levels in ambulatory patients with moderately advanced multiple sclerosis**

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**Background:** People with MS (pwMS) are at risk of osteoporosis due to immobility and repetitive steroid use. PwMS are also at risk of falls due to physical, visual and/or cognitive disability. Vitamin D deficiency is associated with both disease progression in MS and increased risk of osteoporotic fractures.

**Objectives:** To assess fracture risk, fall risk and serum vitamin D in ambulatory patients with moderately advanced MS; to compare the utility of 3 fracture risk scoring methods and a fall risk tool.

**Methods:** Consecutive pwMS aged 18-75 years with Expanded Disability Severity Scale (EDSS) score of 3.0-6.5 attending the MS clinic were invited to participate in the study involving measurement of serum vitamin D level and administration of an amalgamated questionnaire containing all question items included in the Fracture Risk Assessment Tool (FRAX), QFracture, an MS-Specific Fracture Score (MSSFS) and the Johns Hopkins Fall Risk Assessment Tool (JHFRAT). Data was analysed using SPSS v24.

**Results:** Of a total of 26 pwMS (n=13, RRMS; n=11, SPMS; n=2 PPMS), 58% were female, median age 51 years, median MS disease duration 12.5 years, median EDSS 5.0. Only 15% (4/26) had ever received specific advice on bone protection in MS. 46% had a serum vitamin D level (overall median 96nmol/l, range 16-315) below the threshold (70nmol/l) required for optimal bone health. No significant associations existed between serum vitamin D and fall risk score, prior falls, fracture risk scores or prior fracture.

Although there were moderate to strong correlations between each fracture risk score with one other score (MSSFS and QFracture,  $r_s=0.484$ ,  $p=0.01$ ; MSSFS and FRAX,  $r_s=0.83$ ,  $p<0.0001$ ; FRAX and QFracture,  $r_s=0.835$ ,  $p<0.0001$ ), there was a wide variation in proportion of patients exceeding threshold for intervention (bone mineral density measurement +/- anti-osteoporotic therapy) across the 3 fracture scores (54% MSSFS; 38% FRAX; 19% QFracture;  $p<0.0001$ ).

46% (12/26) reported prior falls. Using JHFRAT, 54% (14/26) were categorised as having moderate fall risk. JHFRAT did not distinguish between patients with and without prior falls ( $p=0.671$ ). JHFRAT showed a moderate correlation with MSSFS ( $r_s=0.505$ ,  $p<0.0001$ ) but not with FRAX or QFracture.

**Conclusion:** These results highlight the underestimated importance of assessing bone health in pwMS. Serial serum vitamin D measurements may be of value. Choice of fracture and fall risk assessment tools for pwMS should be further studied.

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## EP1438

**Multiple sclerosis and the risk of venous thrombosis: a systematic review**

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**Objective:** Our aim is to estimate the incidence of Venous Thromboembolic (VTE) disease in Multiple Sclerosis (MS) patients compared to those without MS, through a critical and systematic review of the literature. Additionally, if data is available we aim to assess if MS clinical features, such as MS type, disease duration and severity, are associated with a higher risk of VTE.

**Methods:** We searched PubMed and EMBASE. The records were initially screened using their titles then abstracts. Full text articles were read by two independent reviewers to assess if they met the following inclusion criteria: study population consists of patients with a confirmed diagnosis of MS according to the accepted diagnostic criteria at the time of the study; comparison group consists of patients with no diagnosis of MS; clinical outcomes include incidence rates of VTE events with Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) diagnostic strategies clearly stated, as well as risk ratios of MS vs non-MS. Data was extracted by one reviewer using a standardized form and verified by a second. A metaanalysis was carried out using OpenMeta[Analyst] software. Each study was critically appraised using the Newcastle-Ottawa Quality Assessment scale.

**Results:** We included 7 articles and carried out a metaanalysis on 6. The analysis showed MS to be associated with a 1.907 (95% confidence interval 1.676-2.171) increased risk of VTE. Studies varied greatly in design and quality. MS severity, secondary progressive MS, disability, steroid use, spasticity and antidepressant use were found to be associated with an increased risk of VTE.

**Conclusion:** This review highlights just how little research there is on this topic. The limited literature suggests that MS may confer an increased risk of VTE. It also suggests MS related factors such as spasticity, steroid use and disability may be associated with a higher risk of VTE in MS patients, but there is still uncertainty. More studies are needed to recognize these particular risk factors to allow risk stratification and identification of particular MS patients that may potentially benefit from VTE prophylaxis.

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#### EP1439

##### **Low bone mineral density in neuromyelitis optica spectrum disorder: correlation with disease severity and body mass index**

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**Introduction:** Neuromyelitis optica (NMO) is a female-predominant autoimmune disorder of CNS with a disease-specific antibody against CNS water channel, aquaporin 4 (AQP4). Patients with NMO experience reduced mobility and are susceptible to falls; moreover, many patients are being treated with glucocorticoids which are known risk factors for osteoporosis. However, there is no study for osteoporosis in NMO. This study aims to investigate the frequency of the osteoporosis and the association between bone mineral density (BMD) and disease disability, glucocorticoid use, or disease duration in NMO.

**Methods:** Bone mineral density (BMD) was measured by dual x-ray absorptiometry in patients, who were diagnosed as NMO spectrum disorder (NMOSD) with anti-AQP4 antibody (anti-AQP4). We analyzed clinical features including the Expanded Disability Status Scale (EDSS) score, cumulating steroid dose, annual relapse rate (ARR), and body mass index (BMI).

**Results:** A total of 37 patients (mean age, 48.89±13.98 years; F:M=36:1) were included in this study. The disease duration at the time of BMD test was 8.86±6.57 years. BMD was correlated with the EDSS score ( $r^2 = 0.172$ ,  $p=0.10$ ) and the BMI at the time of BMD test. ( $r^2 = 0.078$ ,  $p=0.016$ ) However, BMD was not correlated with age, disease duration, and the total dosage of steroid. The incidence of osteopenia and/or osteoporosis was significantly higher, compared to normal population, according to the ages (10-19 years, 67% vs %; 20-29 years, 63% vs %; 30-39 year, 86% vs %; 40-49 years, 86% vs %; 50-59 years, 86% vs %; 60-69 years; 67% vs %).

**Conclusion:** Our study showed that NMO patients had higher frequency of low bone mass compared with normal population, even at an early age and BMD was correlated with disease severity and BMI. Since low BMD was present in NMO patients at their early age, NMO patients should be screened for early detection and treatment, particularly with high disease severity and low BMI.

#### **Disclosure**

nothing to disclose

#### **EP1440**

##### **Reverse takotsubo in a severe case of neuromyelitis optica**

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**Background:** Takotsubo is very rare in neurological diseases, where a release of catecholamine due to bulbar vegetative areas lesions could lead to sympathetic overactivation. Demyelinating diseases were not classically associated with takotsubo cardiomyopathy. Recently, Androdias et al. reported five cases of multiple sclerosis (MS) with takotsubo associated with a new demyelinating lesion in the medulla oblongata on brain MRI were reported.

**Objective:** To report the case of a reverse takotsubo during an acute tetraplegia and brainstem syndrome revealing neuromyelitis optica (NMO).

**Results:** A 49 year-old woman without significant medical history, developed tetraparesia with dysarthria, dysphagia, oculomotor impairment, urine retention, tachycardia and hypotension leading to mechanical ventilation over one week. CSF analysis revealed a lymphocytic cellular reaction (210/mm<sup>3</sup>), an elevated protein level (2 g/L) and presence of oligoclonal bands with elevated IgG index. Electrocardiogram showed a sinus tachycardia without ST-segment modification associated with elevated troponine levels (1327 ng/L). Echocardiography revealed a severe left ventricular dysfunction (ejection fraction of 20%) with basal akinesia and residual apical mobility, typical of reverse takotsubo. Cardiac MRI showed no argument in favor of myocardial ischemia or myocarditis. MRI revealed the presence of longitudinal extensive transverse myelitis (LETM), lesions of the medulla oblongata, corpus callosum and left temporal lobe with gadolinium enhancement. Anti-aquaporin 4 antibodies (anti-AQP4) were positive, confirming the diagnosis of NMO. Cardiac dysfunction fully recovered in three days while neurologic outcome at 2 months was very poor despite plasma exchange, high dose steroids and Rituximab.

**Discussion:** To our knowledge, this is the first reported case of takotsubo occurring in NMO. Only two cases of LETM with brainstem involvement and takotsubo were previously described in a 10 year-old boy and in a 27 year-old woman, without confirmation of NMO diagnosis. The five cases of MS with takotsubo recently reported were also younger (16-27 year-old) with good neurological recovery. As in our case, reverse takotsubo was observed in 3 of them.

**Conclusion:** This observation suggests that MS and NMO share some common features in relationship with takotsubo, possibly due to the localization of inflammatory lesions in the medulla oblongata in both demyelinating diseases.

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### EP1441

#### **Bone health in neuromyelitis optica spectrum disorder: association with disability, steroid treatment, or leisure time exercise?**

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**Introduction:** Patients with multiple sclerosis (MS) are at high risk for bone loss and/or fracture, which are one of the major cause of morbidity and mortality. However, the prevalence and risk factors for bone loss in neuromyelitis optica spectrum disorder (NMOSD) has not been evaluated, yet.

**Methods:** We performed a cross-sectional survey in two major referral center for NMOSD in Seoul, Korea from April 2006 to May 2017. Fifty-nine NMOSD patients with aquaporin-4 IgG and twenty MS patients were included. Self-report questionnaire (leisure time exercise, history of fracture, comorbidity, menopause, and lifestyle) and laboratory test (bone mineral density (BMD) using central dual energy X-ray absorptiometry, serum level of vitamin D, hormones, and bone turn over markers) were performed. Diagnosis of low bone mass was made using International Society for Clinical Densitometry and World Health Organization criteria. The 10-year probability of hip or osteoporotic fracture was calculated using the Fracture Risk Assessment Tool (FRAX) score.

**Results:** The NMOSD group had poorer bone health than MS group in terms of the prevalence of low bone mass (67.8 % vs 10%,  $p < 0.0001$ ) and the FRAX score  $\{12.85 \pm 10.67$  (mean  $\pm$  standard deviation) vs  $4.54 \pm 2.86$ ,  $p < 0.0001$ }. In NMOSD group, multivariate linear regression analysis indicated that only the duration of oral steroid therapy ( $p = 0.030$ ) was significantly associated with the BMD of patients. However, their BMD were not associated with the expanded disability status scale, degree of leisure time exercise, daily or cumulative dose of the oral steroid treatment.

**Conclusions:** The proportion of NMOSD patients with reduced bone mass can be higher than in MS. The BMD in NMOSD is disproportionate to their disability from disease, reduced physical activity nor dosage of daily oral steroid, rather consistent with the duration of oral steroid therapy. Prolonged steroid treatment reduces BMD and could result in increased fracture risk. Identifying these risk factors may allow earlier detection and treatment of osteoporosis, minimize future fracture risk, and maintain the functional status of the patients.

### Disclosure

All authors have nothing to disclose

### EP1442

#### **A pilot study evaluating changes in clinical outcomes with weight loss in people with multiple sclerosis**

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**Background:** Overweight and obesity have been correlated with worse clinical outcomes in people with multiple sclerosis (pwMS), but little research has evaluated changes in outcomes with weight loss. Calorie restriction and time-restricted feeding (i.e. daily 16-hour fasts) are two dietary interventions that are associated with weight loss and improved fatigue and metabolic outcomes in the general population. However, whether these diets lead to improvements in symptoms among pwMS is unknown.

**Objective:** To evaluate the effect of weight change due to calorie restriction and time-restricted feeding on patient-reported outcomes (PROs) including fatigue, sleep quality, depression and self-esteem.

**Methods:** We conducted a 6-month pragmatic pilot study of either calorie restriction or time-restricted feeding in 43 pwMS who were being treated with natalizumab at the Johns Hopkins MS Center. At months 0, 3 and 6 weight and waist and hip circumference were collected. Participants provided information on fatigue (MS-specific PROMIS short-form), sleep (Pittsburgh Quality Sleep Index), and depression (emotional well-being components of the functional assessment of MS [FAMS]) at each time point. We assessed whether changes in anthropometric measures were associated with changes in PROs using linear regression models adjusting for age and gender.

**Results:** Of the 43 participants (86% female), 21 (48.8%) of the 38 who have completed to date lost weight over 6 months (4 of the 5 who will soon complete had lost weight at 3 months), with median weight change of -1.40kg (interquartile range [IQR]: -3.2 to 1.25kg) and median change of waist circumference of -0.25cm (IQR: -2.47 to 1.25). Change in waist circumference was associated with changes in fatigue scores, where a 5 cm decrease (or increase) in waist circumference was associated with an average decrease (or increase) of 1.85 points in fatigue severity (95% CI: -3.41 to -0.26;  $P = 0.02$ ). Similarly, each 5 kg decrease in weight was marginally associated with a 2.24-point decrease in fatigue score (95% CI: -4.52 to 0.06;  $P = 0.09$ ). Changes in weight or waist circumference were not associated with changes in sleep or depression.

**Conclusions:** In this pilot study of various fasting-mimicking diets, a reduction in waist circumference was associated with improvements in fatigue. Further studies investigating the impact of weight reduction, and mechanisms by which it is achieved, on classical MS endpoints and symptoms are needed.

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#### EP1443

##### The link between dysautonomia and depression in multiple sclerosis

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**Background and aims:** Recently it has been suggested that the dysregulation in the neurovisceral integration of cardiovascular modulation can lead to many multiple sclerosis (MS)-related clinical symptoms like depression, fatigue and sleep disorders, migraine, osteoporosis and cerebral hemodynamic impairments. Furthermore, both adrenergic and cholinergic dysfunctions may play roles in the pathology of MS depression. The aim of the present study was to investigate possible association between autonomic dysfunction and depression in MS.

**Design/methods:** In this study, 44 patients with MS were included (30 females, mean age 37.18±10.93), 37 of them (group 1) had clinically isolated syndrome (CIS) or relapsing remitting MS (RRMS) and 7 (group 2) had primary progressive (PPMS) or secondary progressive (SPMS) MS. All patients filled the Beck depression scale (BDI) and Epworth Sleepiness Scale (ESS). The following autonomic tests were performed: heart rate and blood pressure responses to the Valsalva maneuver, heart rate response to deep breathing (RSA), and blood pressure response to passive tilt. All tests were interpreted in the form of the composite autonomic scoring scale (CASS) through adrenergic and cardiovagal indices.

**Results:** Patients from group 2 had significantly higher BDI compared to patients from group 1 (median 16 vs. 7,  $p=0.002$ ). There was no statistically significant difference in two groups between frequencies of pathological values of CASS indices (score >0). Both adrenergic and cardiovagal indices correlated with EDSS ( $r_s$  0.394,  $p<0.05$  and  $r_s$  0.495,  $p=0.001$ ).

Patients with pathological adrenergic index had higher BDI score in comparison with patients with normal index (8 vs. 4.5,  $p<0.05$ ), while there was no difference between patients with pathological and normal cardiovagal index.

For group 2, there was statistically significant correlation between BDI scale and adrenergic and cardiovagal indices ( $r_s=0.797$ ,  $p<0.05$ ; and  $r_s=0.775$ ,  $p<0.05$ ), while there was no correlation for patients from group 1.

**Conclusion:** These results suggest possible association between autonomic dysfunction and depression in MS patients. Further studies are encouraged in order to further elucidate this association.

#### Disclosure

Jelena Drulovic serves on scientific advisory boards for Bayer Schering Pharma, Merck Serono, Teva, Genzyme, a Sanofi Company, and received honoraria for speaking from Merck Serono, Teva, Bayer Schering, Genzyme, a Sanofi Company, Medis, Roche; and has also received research grant support from the Ministry of Education and Science, Republic of Serbia (project no. 175031).

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#### EP1444

##### Tobacco, alcohol, drug use and comorbidity issues in multiple sclerosis (MS): a pilot study

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**Background:** MS is a complex illness with the wide range of symptoms. The MS subtype can be categorized, however, individual disease characteristics are variable. Comorbidity and other individual features such as smoking, alcohol or drug use status in MS patients may contribute to the factors associated with the outcomes, disability levels and the burden of the disease.

**Objectives:** We evaluated the frequencies of tobacco, alcohol, drug use together with existence of other diseases than MS in our study group. Moreover, we explored the relationship between demographic and clinical MS characteristics and smoking, alcohol or drug use status, levels of fatigue, subjective quality of life (QOL) and various comorbidities.

**Materials and methods:** Totally, 125 patients filled in the questionnaire about tobacco, alcohol, drug use together with data about other diseases than MS and the SF-36 scale. Two measures of physical (PCS) and mental (MCS) health were calculated, and the fatigue was evaluated in the 10-point scale. Demographic and clinical data with the Expanded Disability Status Scale (EDSS) scores were collected.

**Results:** Women comprised 70.4% of the group, and men-29.6%. The mean of the age was  $41.1 \pm 11.8$  years. The mean EDSS score was  $2.92 \pm 1.32$ . The majority of the patients had a relapsing-remitting MS (97.6%). Firstly, 20% of patients had arterial hypertension (AH), 8.8% had dyslipidemia, 1.6% had diabetes mellitus (DM), and 5.6% - pulmonary diseases. Secondly, 16% reported depression, and 12% - anxiety disorder. In total, 15% of patients were smoking, and 2.4% reported drug use. The mean alcohol use was  $1.14 \pm 2.12$  alcohol units per month. The mean scores of PCS were  $53.06 \pm 19.83$ , and of MCS  $53.14 \pm 18.26$ , accordingly. The mean score of fatigue was  $6.02 \pm 2.25$ . There was no association between comorbidity, disease course and EDSS ( $p > 0.05$ ). Fatigue measures were higher in patients with AH, depression and drug use, also measures of PCS were lower in patients with depression and dyslipidemia, and the measures of MCS were lower in patients with depression and anxiety ( $p < 0.05$ ). We found the higher relapses rate in patients with dyslipidemia ( $p = 0.039$ ). There was no association with mean alcohol consumption and clinical MS parameters, QOL and fatigue.

**Conclusions:** Our study showed that comorbidity in MS affects levels of fatigue and subjective QOL. We found the association with relapse rate and dyslipidemia. We plan to continue this study and expand the cohort.

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## EP1445

### Concomitant changes in weight and in sleep quality among people with multiple sclerosis

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**Background:** Weight loss diets are primary recommended treatments for metabolic disease and are often associated with improved sleep. Both sleep and metabolic disorders are overrepresented in people with multiple sclerosis (MS); however, whether weight loss diets are associated with improvements in sleep quality in this vulnerable population is unknown.

**Methods:** We conducted a controlled feeding study of different calorie restriction diets in 36 people with MS for a period of 8 weeks. Energy expenditure was determined using indirect calorimetry, and patients were randomized to receive 1 of 3 diets: a

continuous calorie restriction diet (22% daily reduction in energy needs), an intermittent calorie restriction diet (75% reduction in calorie needs 2 days/week; 100% of daily needs 5 days/week), and a weight-stable diet (100% of daily calorie needs). At baseline and at week 8, participants provided information on sleep by completing the Pittsburgh Quality Sleep Index (PSQI), from which a global sleep quality score was calculated.

**Results:** Of the 36 patients enrolled, 31 (86%) completed the trial. Participants randomized to calorie restriction diets lost an average of 7.3 (SD: 4.6) lbs over 8 weeks; changes in weight did not differ by type of calorie restriction diet ( $P = 0.12$ ). At baseline, participants had median PSQI scores of 7 (interquartile range [IQR]: 3.5 to 8.5) and 19 (53%) participants reported scores indicative of poor sleep quality. Weight loss was marginally correlated with improvements in sleep quality score ( $r = -0.32$ ;  $P = 0.06$ ). Individuals in the top quartile of weight loss - corresponding to a  $\geq 8.2$  lb weight loss - experienced an average 3.99 point improvement in global sleep quality score when compared to individuals in the lowest quartile of weight loss - corresponding to a  $< 3$  lb weight loss (quartile 4 vs. quartile 1 mean reduction in PSQI score = 3.99; 95% CI: 0.58-7.39;  $P = 0.03$ ). Changes in sleep quality did not differ between weight loss diets.

**Conclusions:** This preliminary study suggests that among people with MS, weight loss is associated with improved sleep quality. Subsequent results will assess effects of weight loss diets on changes in fatigue levels.

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## EP1446

### Headache characteristics in multiple sclerosis

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**Objectives:** The objectives of this study were to study the prevalence and characteristics of headache in patients with multiple sclerosis (MS) and to clarify the relationship between headache and MS treatment.

**Method:** 782 MS patients were consecutively admitted. All patients filled out a detailed headache questionnaire and 754 patients were included.

**Results:** Of 754 patients, 515 (68.3%) reported having headache. According to the International Headache Society (IHS) criteria, we detected 202 (39%) suffering from migraine, 103 (20%) suffering from tension-type headache (TTH) and 198 (38%) with medication overuse headache (MOH). Twelve patients (2%) had

unclassified headache. Three hundred and seventy seven patients (73%) were treated with immunomodulators (interferon beta/**glatiramer acetate**), 81 (16%) with fingolimod, 35 (7%) with teriflunamide and 22 (4%) with natalizumab, respectively. One hundred and one (20%) reported that onset of headache occurred prior to onset of MS specific treatment, while 414 (80%) had headaches occurred after therapy. A higher incidence of headache was found in patients treated with immunomodulators. Three hundred and twenty two (62%) patients have never sought help from a physician despite the severity and frequency of headache.

**Conclusion:** In our study, the prevalence of headache MS patients was 68%. The results of this study indicate a possible relationship may exist between headache and MS. Interestingly, MOH was far more prevalent in MS patients than in previously reported community populations.

### Disclosure

nothing to disclose

### EP1447

#### Occurrence of cardiovascular (CV) risk factors and metabolic syndrome (MetS) in multiple sclerosis (MS)

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**Background:** Last years there is an emerging interest on metabolic and CV comorbidities in MS patients, especially on the association of these parameters with outcome and prognosis of MS. It's known that inflammation play a fundamental role in both conditions and maybe by treating MetS or modifying CV risk factors one can reduce the odds for disability and progression of MS.

**Goals:** This study aim to determine the frequency between CV risk factors, metabolic syndrome (according to the criteria of International Diabetes Federation) and MS.

**Methods:** 59 patients (42 males and 17 females, 25 to 60 year-old) with relapsing remitting MS (mean EDSS=3 and mean duration of disease 9 years) under disease modifying treatment were recorded for hypertension, smoking, dyslipidemia, obesity, type 2 diabetes and positive family history for CV disease. Body mass index (BMI), waist circumference and levels of fasting glucose, HDL, LDL cholesterol and triglycerides were also obtained.

**Results:** MetS was evaluated on 22.3% but half of our patients had at least two CV risk factors. Furthermore, abnormal BMI was frequently recorded (overweighed 32.20%, with obesity 16.9%), and 49% of our cohort admitted that they didn't do any gym or physical exercise. Smoking is a frequent habit among MS patients (47.2%) and regarding the family history it is positive for CV risk factors almost at half of them.

**Conclusions:** Metabolic and CV comorbidities in MS are not yet elucidated and future research should be elaborated in order to improve our understanding for the possible interaction in etiology, disability and prognosis of MS.

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### EP1448

#### Effects of systolic blood pressure on brain integrity in multiple sclerosis

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**Background and goals:** Epidemiological findings suggest a relationship between MS clinical outcomes and several cardiovascular comorbidities, including obesity, insulin resistance, dyslipidemia, and hypertension; the latter being the most frequent cardiovascular comorbidity reported in MS. In chronic conditions, cardiovascular comorbidities are associated with decreased quality of life and increased mortality. In MS in particular, comorbidities are associated with delayed diagnosis and increased risk of disease progression. Despite the strong epidemiological evidence, there is a paucity of studies exploring pathophysiological mechanisms to explain the association between MS and cardiovascular comorbidities. In particular, the mechanisms linking MS severity and elevated blood pressure are poorly understood. Here, we aim to establish whether high blood pressure contributes to white-matter injury and brain atrophy in patients with relapsing-remitting multiple sclerosis (RRMS).

**Methods:** Estimates of cerebral fractional anisotropy, grey-matter volume and lesion load were obtained from 3-Tesla MRI in 95 patients with RRMS between December 2013 and July 2015. We used fractional anisotropy voxel-based statistics to establish the effect of blood pressure on white matter tracts. Additionally, we used voxel-based morphometry to study the effect on grey matter integrity. Finally we utilized linear models with log-transformed white matter lesion volume as the dependent variable and systolic blood pressure as the predictor to establish the effect of hypertension on lesion load.

**Results:** 57 female and 38 male patients (mean age 38.9 years, SD 10.5) underwent brain MRI. Only 29.5% had normal blood pressure levels, with 52.6% suffering from prehypertension and 17.9% with hypertension. Increasing systolic blood pressure was associated with damage to posterior white-matter tracts as well as greater levels of grey matter atrophy, in particular in the frontal cortex. Age-adjusted linear regression indicated that neither lesion volume ( $\beta=0.002$ , 95% CI -0.02 to 0.02;  $p=0.85$ ) or lesion number ( $\beta=-0.004$ , 95% CI -0.03 to 0.02;  $p=0.74$ ) were associated with systolic blood pressure.

**Conclusions:** Prehypertension and hypertension are frequent in MS patients. Increased blood pressure is related to white- and grey-matter integrity, both related to MS disability outcomes. These findings suggest attention to the control of blood pressure in MS patients.

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Francisco J. Quintana serves on the editorial board for *Systems Biomedicine*, *Immunologia*, *American Journal of Clinical and Experimental Immunology*, is an associate editor for *Immunology* (UK), is an advisory board member for *Seminars in Immunopathology*; received research support from Harvard Medical School, BADERC, NMSS

Jorge Correale is a board member of Merck-Serono Argentina, Novartis Argentina, Genzyme LATAM, Genzyme global, Biogen-Idec LATAM, and Merck-Serono LATAM. Dr. Correale has received reimbursement for developing educational presentations for Merck-Serono Argentina, Merck-Serono LATAM, Biogen-Idec Argentina, Genzyme Argentina, Novartis Argentina, Novartis LATAM, Novartis Global, and TEVA Argentina as well as professional travel/accommodations stipends.

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#### EP1449

##### Insulin resistance and multiple sclerosis: a pilot study in drug naive patients

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**Objective:** The main objective of our study was to demonstrate whether a dysbalance of glucose and insulin metabolism exist in patients with MS with the natural course of the disease. Our hypothesis is that the metabolic disorder that characterizes state of the insulin resistance (IR) and reduced insulin sensitivity (IS) in untreated patients with MS could play a role in disease progression and degree of functional disability.

**Methods:** The study included 31 patients with relapsing-remitting (RR) MS and 14 healthy controls from the same geographic area matched by age, ethnicity and number of smokers. The glucose tolerance IS, and IR were examined from an oral glucose tolerance test (OGTT) and from basal plasma glucose and insulin levels. The functional disability and disease progression were evaluated by the Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Severity Score (MSSS).

**Results:** MS patients tolerated glucose equally well as the healthy controls. Basal concentrations of insulin were significantly higher in MS group ( $p < 0.05$ ) as well as insulin in 30 min after oral glucose load ( $p < 0.01$ ).

Patients with MS had significantly higher values of homeostasis model assessment indexes of IR (HOMA-IR) ( $p = 0.027$ ;  $p = 0.028$ ). The percentage of IS (HOMA2 %S) and whole body IS index (ISI Matsuda) showed significantly lower values in MS patients than in controls ( $p = 0.005$ ;  $p = 0.001$ ).

#### Disclosure

Nothing to disclose

#### EP1450

##### Interaction between comorbidities and use of disease modifying treatment in impact on quality of life in a Regional Multiple Sclerosis Registry

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**Background:** Studies have shown that comorbidities impact health outcomes and quality of life (QoL) in the multiple sclerosis (MS) population. However, less is known about how use of disease modifying treatment (DMT) mitigates the impact of comorbidity on QoL.

**Objective:** To determine which specific comorbidities impact QoL and if DMT use reduces the impact of comorbidities on QoL among participants in the Pacific Northwest Multiple Sclerosis Registry (PNWMSR).

**Methods:** PNWMSR participant survey data from 2011 to 2016 was used. Participants who had relapsing disease were included. Those who had progressive MS, reported use of more than one DMT, were on their reported DMT for less than six months, or had not reported duration of DMT were excluded. Comorbidities included were cardiovascular disease, respiratory disease, smoking, cancer, thyroid disease, gastrointestinal (GI) disease, depression and obesity. Chi-square tests were used to determine differences in the prevalence of comorbidities among those who used and did not use DMT. Physical and psychological QoL was measured using the Multiple Sclerosis Impact Scale (MSIS), with higher scores indicating more severe impact. Multiple linear regression, adjusting for participant characteristics, was used to determine the impact of comorbidities and DMT use on physical and psychological QoL scores. Interactions between DMT use and comorbidities that significantly impacted MSIS were tested using Type III F-tests to determine whether DMT use moderated the effect of comorbidities on QoL.

**Results:** Survey data from 1,163 participants were included in the final analysis. Cancer, thyroid and GI disease were significantly more prevalent among participants not on DMT. Depression was significantly more prevalent among those on a DMT. Physical MSIS scores worsened with depression ( $\beta = 3.26$ ;  $p < .001$ ), respiratory diseases ( $\beta = 2.59$ ;  $p = .001$ ), and thyroid diseases ( $\beta = 2.55$ ;  $p = 0.04$ ). Psychological MSIS scores worsened with depression ( $\beta = 4.37$ ;  $p < .001$ ), thyroid disease ( $\beta = 2.17$ ;  $p = .002$ ), and smoking ( $\beta = 1.12$ ;  $p = 0.04$ ). All interactions between DMT use and comorbidities were not significant.

**Conclusions:** The prevalence of comorbidities differed based on DMT use. Depression was highly prevalent among DMT users and had the largest impact on psychological and physical QoL in this regional cohort. The use of DMT had no significant moderating effect on the impact of comorbidities on physical or psychological QoL.

#### Disclosure

T. Stuchiner, L. Lucas, E. Baraban and C. Chen have no conflict of interest to report.

S. Cohan has either served on advisory boards or steering committees for Biogen, Novartis, Sanofi Genzyme, and Mallinckrodt; have received research support from Biogen, Novartis, Sanofi

Genzyme, Opexa, Teva, Mallinckrodt, and Roche; have received speaker honoraria from Biogen Idec, Novartis, Sanofi Genzyme and Acorda.

#### EP1451

##### **Risk of developing cancer and its impact on patients with multiple sclerosis under treatment with immunomodulators**

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**Introduction:** The incidence of multiple sclerosis (MS)-associated neoplasms was not a frequent report before the advent of immunomodulators (IMDs). In fact, it was assumed that MS granted a certain protective effect against the risk of developing cancer (Ca). With the advent of IMDs, the potential association of MS with cancer events was first noted.

To date, the relationship between the impact of Ca and of cancer treatments with the progression of MS remains to be established. **PURPOSES:** To analyze the characteristics of a group of patients with Demyelinating Diseases (DD) who developed cancer, the therapeutic behaviors and their progression.

**Methods:** We conducted a retrospective observational study of 1,192 patients with DD, and assessed 27 patients who developed cancer during the progression of their baseline disease. We evaluated the type of DD, the type of cancer, age at onset, treatments used, and progression of the DD within 2 years of cancer onset: presence of relapses, changes in the EDSS and MRI.

**Results:** n=27 patients with DD and Ca. Age at diagnosis: 28.9years and age at Ca onset: 47years. Clinical form: n: RRMS 21; SPMS 3; NMO 2; RIS 1.

IMDs: 21 patients. IMDs discontinued: 12 patients.

- n=cancer types: 6=breast; 5=thyroid; 7=gynecological; 3=colorectal; 2=skin; 4=others. 4=multiple.

- n=cancer therapy: 20=surgery; 7=chemotherapy; 3=radiotherapy; 8=combined; 1=none.

MS behavior in cancer patients:

- Relapses: 4=Yes; 14=No; 6=No data.

- Changes in EDSS: 2=Better; 14=No changes; 11=Worse (3=dead)

- Changes in MRI: 14=No changes; 3=New lesions; 10=No data

**Conclusion:** Only 4 patients had relapses after the development of cancer. Sixteen patients had the same or better scores at EDSS and over half of them evidenced MS progression in MRI. The coexistence of two potentially severe diseases (Ca and MS) would not necessarily involve a more unfavorable progression of MS.

#### **Disclosure**

Curbelo, María Celeste: nothing to disclose.

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Carrá, Adriana J: nothing to disclose.

#### EP1452

##### **Cognitive profiles in Hong Kong Chinese with relapsing and progressive multiple sclerosis**

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**Background:** We evaluated the cognitive profiles in Hong Kong Chinese with multiple sclerosis (MS).

**Methods:** We recruited subjects from the Hong Kong Multiple Sclerosis Registry. We administered a 45-minute neuropsychological battery, covering verbal learning and memory, processing speed, selective attention, executive function, visual perception, simple auditory attention span, and auditory working memory. Hong Kong version of Montreal Cognitive Assessment (HK-MoCA) was performed as a cognitive screening tool. Fatigue and physical disability were assessed by Modified Fatigue Impact Scale (MFIS) and Expanded Disability Status Scale (EDSS), respectively. Neuropsychological test scores were converted into z-scores using normative data for local Chinese, with impairment defined as z-score < -1.0.

**Results:** Fifty-five subjects (87% females; 78% relapsing MS, 13% PPMS, and 9% SPMS) were recruited. The mean age, education, and EDSS were 38.5±11.0 years, 13.6±3.32 years, and 3.6±2.6, respectively. Relapsing MS subjects were younger (36 vs. 47 years), better educated (14 vs. 11 years), and less disabled (EDSS 2.5 vs. 6.75) than progressive MS (p<0.05). Overall, 52/55 (95%) subjects had cognitive impairment(s): verbal learning and memory-62%, executive function-50%, processing speed-50%, auditory working memory-49%, visual perception-43%, selective attention-37%, simple auditory attention span-16%. Multiple (≥3) impaired domains are found in 54% subjects; progressive MS subjects had worse cognitive performance (p<0.05). Cognitive impairment was strongly correlated with high EDSS, low HK-MOCA and education years (p<0.01). In multivariate regression model, HK-MOCA predicted multiple cognitive domain impairments (OR 0.70, 95% CI 0.50-0.98, p=0.035). At a cut-off score of 24, HK-MOCA has sensitivity of 81% and specificity of 71% (AUC 0.80). MFIS was not predictive of impaired cognitive performance.

**Discussions:** Cognitive impairment is highly prevalent among Chinese MS patients, affecting one or more cognitive domains in 95% patients. HK-MOCA is useful to screen for subjects with multiple impaired cognitive domains. Cognitive fatigue may be compensatory to preserve cognitive function.

#### **Disclosure**

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#### EP1453

##### **Interaction between comorbidities and use of disease modifying treatment in impact on disability status in a regional multiple sclerosis registry**

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**Background:** Comorbidities can have a negative impact on disability in the multiple sclerosis (MS) population. However, disease modifying treatments (DMT), which prevent disease progression, could potentially moderate the effect of comorbidities. Little is known about the relationship between DMT use and comorbidities and its impact on disability.

**Objective:** To determine the impact of comorbidities and DMT use on disability in participants in the Pacific Northwest Multiple Sclerosis Registry.

**Methods:** Participant survey data collected between 2011 and 2016 were used. Participants who had progressive disease, reported use of more than one concurrent DMT, were on DMT less than six months if used DMT, or did not report time on DMT were excluded. Comorbidities included were cardiovascular disease, respiratory disease, smoking, cancer, thyroid disease, gastrointestinal (GI) disease, depression and obesity. Disability status was measured using the Patient Determined Disease Step (PDDS) score and disability was categorised as follows: none (0), mild (1 or 2) and moderate to severe (3 to 7). Polytomous logistic regression, adjusting for participant characteristics, was used to determine the impact of comorbidities and DMT use on reported disability status. Interactions between significant comorbidities and DMT use were tested in the regression model to investigate moderating effects.

**Results:** Survey data from 1,163 participants were analysed. Depression (33.6%, n=391), cardiovascular disease (29.0%, n=337), and respiratory disease (11.6%, n=135) were the most prevalent comorbidities. Participants were more likely to be moderately/severely disabled when they reported GI disease (Adjusted Odds Ratio (AOR) =4.09; p=.001), depression (AOR=3.20; p<.001), cardiovascular disease (AOR=2.21; p<.001), smoking (AOR=1.85; p=.004), and respiratory disease (AOR=1.43; p=0.05). For participants who smoked, DMT users had a decreased likelihood of being moderate or severely disabled (AOR=0.32; p=0.01). However, DMT use increased the likelihood of moderate to severe disability for those with depression (AOR=3.10; p<.001) and respiratory disease (AOR=3.67; p<.001). DMT had no moderating effect on those with GI or cardiovascular disease.

**Conclusions:** Results suggest the effects of smoking and depression on disability are moderated by DMT use, resulting in differing effects on disability. Further research is needed to understand the underlying mechanisms for these differences.

## Disclosure

L. Lucas, T. Stuchiner, E. Baraban and C. Chen have no conflict of interest to report. S. Cohan has either served on advisory boards or steering committees for Biogen, Novartis, Sanofi Genzyme, and Mallinckrodt; have received research support from Biogen, Novartis, Sanofi Genzyme, Opexa, Teva, Mallinckrodt, and Roche; have received speaker honoraria from Biogen Idec, Novartis, Sanofi Genzyme and Acorda.

## Pathology

### EP1454

#### Characterization of TSPO expression by conventional and multiplex immunohistochemistry in marmoset EAE

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The 18 kDa translocator protein is a mitochondrial transmembrane protein that is lowly expressed in the healthy CNS but strongly upregulated in CNS injury and thus of interest as a biomarker of

neuroinflammation. TSPO is abundantly expressed in activated microglia and macrophages, and numerous studies have shown the transporter to be highly upregulated in inflammatory CNS lesions in multiple sclerosis (MS) and animal models of experimental autoimmune encephalomyelitis (EAE). Marmosets are small New World monkeys of particular interest for their neurological similarity to humans, which renders them a powerful model of neuroinflammatory disease. Most crucially, marmosets exhibit white matter-grey matter ratios similar to those of humans, and EAE marmosets manifest lesions that are pathologically and radiologically similar to lesions seen in MS patients. However, TSPO expression in marmoset EAE remains largely uncharacterized.

To better understand the utility of TSPO as a biomarker of inflammation in EAE, this study seeks to characterize the cellular localization of TSPO in marmoset EAE by immunohistochemical analysis of pathological brain and spinal cord tissues. Specifically, this study characterizes the cellular localization of TSPO and the immunophenotype of TSPO+ microglia/macrophages at different stages of lesion development. Our study confirms the common marmoset model of EAE to recapitulate the expression of TSPO in microglia and macrophages that is observed in rodent models. In early lesions that are less than 4 weeks old (as determined by serial magnetic resonance imaging scans), TSPO is expressed in over 90% of Iba1+ microglia/macrophages, particularly in the hypercellular nodules observed at the core of many lesions. In these Iba1+TSPO+ cells, TSPO is frequently co-expressed with MRP14, a marker of early activation, and CD74, the invariant chain of HLA-DR. In older lesions (over 7 months old), TSPO expression is observed in less than 15% of Iba1+ cells, and the percentage of Iba1+TSPO+ cells co-expressing MRP14 or HLA-DR is also observed to decrease. These findings give insight into the timecourse of TSPO expression in neuroinflammation, which has significant implications for its clinical utility as an imaging target in the monitoring of neuroinflammatory disease.

## Disclosure

Irene Falk: Nothing to disclose.

### EP1455

#### Markers of intestinal permeability defects are related to clinical activity in early multiple sclerosis

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**Background:** Recent evidence suggests that the intestine might be an early site of MS disease in response to environmental toxins. Disruption of the intestinal barrier integrity is one potential mechanism for which the noxious luminal products (including bacterial lipopolysaccharide, LPS) induces mucosal immune dysfunction and systemic immune activation, which might trigger the development of MS. The interaction of LPS with factors such as LPS binding protein (LBP) and soluble CD14 (sCD14) are key events on LPS-induced activation of the innate immune system. Thus, LBP and sCD14 are considered as indirect markers of bacterial translocation.



**Aims:** To explore the utility of intestinal permeability markers (intestinal fatty acid binding protein, I-FABP) and microbial translocation (LBP and sCD14) in early MS.

**Methods:** Thirty six patients were included (19 early MS, 3 RIS, and 14 patients affected by other CNS diseases different from MS). Blood samples were collected with a mean delay from the MS onset to the blood test: 5,6 month, and all were free of immunomodulatory treatment. Clinical and MRI data were collected and correlated with the biological molecules. Serum levels of LBP, sCD14 and I-FABP were measured by commercial ELISA kit.

**Results:** Serum levels of LBP, sCD14 and I-FABP did not differ between the 3 clinical phenotypes. Considering the MS group, levels of LBP positively correlated with the relapse rate throughout the follow up ( $r=0.54$ ,  $p=0.02$ ). Findings are in accordance with both the LBP role in activating innate immune responses, and the involvement of the innate immune system in the acute inflammatory events in MS.

**Conclusions:** LBP could have utility in the clinical activity to improve the prediction of relapse risk in early MS patients. Further research should be performed in a larger cohort of patients in order to confirm these results.

## Disclosure

Nieves Tellez has nothing to disclose,  
Patricia Mulero has nothing to disclose,  
Natan Redondo has nothing to disclose,  
MJose Neri has nothing to disclose,  
M<sup>a</sup>Luisa Nieto has nothing to disclose,  
Marita Hernandez has nothing to disclose,  
Beatriz Gutierrez has nothing to disclose,  
Isabel Gallardo has nothing to disclose

## EP1456

**Anti-AQP4 autoantibody, C5a, neutrophils and glutamate - four necessary, related components essential for neuromyelitis optica inflammation**

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Neuromyelitis optica (NMO) is a neuroinflammatory disease characterized by severe optic neuritis and longitudinally extensive transverse myelitis. For many years NMO was believed to be a rare variant of multiple sclerosis (MS). In contrast to MS, autoantibodies against aquaporin-4 (AQP4), a water channel densely expressed on astrocytic end-feet, has been detected exclusively in sera from patients with NMO. Many studies have suggested that AQP4 autoantibodies are pathogenic, but the precise mechanism triggering inflammation and astrocyte impairment following anti-AQP4 Abs binding remains unknown. Some *in vivo* studies advocated for the role of complement system and neutrophils activation, while other highlighted glutamate pathological distribution as the main mechanism.

In this study we showed direct evidence of pathogenicity of the AQP4 Abs-positive serum derived from NMO patient, which by consecutive action of anti-AQP4 Abs, complement system and neutrophils triggered the reaction towards astrocytes. Based on our results we postulated the new theory about NMO pathogenesis which assumes that, there are two parallel-complementary mechanisms which can be initiated by anti-AQP4 autoantibody. First one was dependent on the complement cytotoxicity *via* C5b-C9 complex formation, and the second one was dependent on the reverse of astrocyte glutamate pump into extracellular space on the C5a-preactivated neutrophils. As a consequence, part of the astrocytes was destroyed, however a certain population of astrocytes polarized into proinflammatory cells which characterized pathological glutamate removal from extracellular space.

## Disclosure

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Paweł Piątek, Małgorzata Domowicz, Natalia Lewkowicz, Patrycja Przygodzka, Mariola Matysiak, Katarzyna Dzitko, Krzysztof W. Selmaj and Przemysław Lewkowicz: nothing to disclose.

## Experimental models

### EP1457

**Influence of CBD in mesenchymal stem cells therapy in adoptively transferred experimental autoimmune encephalomyelitis: an *in vivo* and *in vitro* study**

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**Background:** Mesenchymal stem cells (MSCs) are promising candidates for MS therapies due to their anti-inflammatory properties. Although little is known about endocannabinoid system in MSCs, it has been described that Cannabidiol (CBD), a non-psychotropic cannabinoid, might enhance the therapeutic effect of these cells.

**Objectives:** To explore the influence of CBD in MSCs cultures as well as to test the ability of CBD to improve MSCs therapeutic effect in adoptively transferred EAE (at-EAE).

**Methods:** At-EAE was induced in C57BL/6 mice by inoculation of encephalitogenic cells. Treatment consisted in  $0.5 \times 10^6$  bone marrow MSCs infused twice a week. Cell infiltration, axonal loss and demyelination were analyzed *ex vivo* by confocal microscopy in lumbar spinal cords.

*In vitro*, cannabinoid receptors were determined in MSCs and encephalitogenic cells by confocal microscopy and flow cytometry. Toxicity and cytokines production mediated by CBD in co-cultures of MSCs and encephalitogenic cells were revealed by

MTT and ELISA respectively. Influence of CBD in capacity of differentiation and migration of MSCs was also evaluated. Additionally, clinical parameters in at-EAE animals treated with MSCs in combination with CBD (50mg/kg/d) were studied.

**Results:** MSCs treatment ameliorated clinical signs of at-EAE accompanied by a reduction of cell infiltration and axonal damage. *In vitro*, CB1, CB2 and GPR55 receptors analysis revealed a scarce surface expression in MSCs compared to encephalitogenic cells. Furthermore, MSCs and encephalitogenic cell co-cultures, showed a reduced viability of encephalitogenic cells, a reduction in IFN- $\gamma$  and GM-CSF and an increase in CXCL-10 and IL-6 cytokines.

Addition of CBD in co-cultures resulted in a decrease in IL-6 production and adipogenic differentiation whereas migratory capacity was not modified in MSCs.

CBD concomitant treatment with MSCs cells caused a higher trend to reduce clinical signs in at-EAE compared to MSCs-treated group.

**Conclusions:** MSCs reduced clinical signs *in vivo*, diminishing neuro-inflammation and infiltration in at-EAE, concurrently with a modulation in viability and cytokines production in encephalitogenic cells *in vitro*. The CBD influence in IL-6 cytokine production might be related to the therapeutic effect showed in the concomitant *in vivo* treatment. The beneficial effect of the combination of CBD and cellular therapy opens new possibilities for the treatment of neurodegenerative disorders.

## Disclosure

Coral González García: nothing to disclosure

Ruth García Hernández: nothing to disclosure

Irene Moreno Torres: nothing to disclosure

Lucía Campos Ruíz: nothing to disclosure

María José Coronado Albí: nothing to disclosure

Arantxa García Grande: nothing to disclosure

Antonio García-Merino: has received compensation for travel expenses, speaking honoraria and consultation fees from Bayer, Merck, Teva, Biogen Idec, Novartis, Roche, Almirall, Sanofi-Aventis and Genzyme

Antonio Sánchez López: nothing to disclosure

## EP1458

**Increased post-translational lysine acetylation of myelin basic protein is associated with peak neurological disability in a mouse experimental autoimmune encephalomyelitis model of multiple sclerosis**

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**Background:** Post-translational modifications (PTM) that decrease the positive charge of myelin basic protein (MBP) are implicated in myelin damage and multiple sclerosis (MS). The citrullination of the arginine residues on MBP has been identified as a potential cause.

**Objective:** To identify changes in lysine and arginine PTMs to MBP in spinal cord tissue and correlated these changes to neurological disability scoring as a marker for the degree of myelin damage.

**Methods:** Increases in lysine acetylation and methylation of MBP isolated obtained from an experimental autoimmune encephalomyelitis (EAE) animal model of MS were assessed by using a mass spectrometry assay.

**Results and conclusion:** We show lysine acetylation increases by two-fold on MBP during the peak inflammatory phase post-EAE induction. We also find that MBP mono- and dimethyl-lysine, as well as asymmetric dimethyl-arginine are significantly elevated at peak EAE disability. These findings suggest that lysine PTM of MBP may play a pivotal role in the neurological disability that is associated with MS. Histone deacetylase inhibitors have been previously shown to improve neurological disability. Here we show that treatment with trichostatin A significantly improves the neurological disability of EAE mice through some other mechanisms other than increasing acetylation.

## Disclosure

The Authors declare no conflict of interest.

## EP1459

**Oleanolic acid protects against intestinal permeability defects and its causes in experimental autoimmune encephalomyelitis**

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**Background:** Multiple sclerosis (MS) is a pro-inflammatory demyelinating disease of the central nervous system, in which oxidative stress also plays an important role. Accumulating evidence from studies in patients and animal models (experimental autoimmune encephalomyelitis, EAE) suggest that disruption of intestinal homeostasis may affect disease progression, thus representing a potential therapeutic target in MS. The triterpene, oleanolic acid (OA), has proven effective protecting blood-brain barrier integrity in EAE via anti-oxidant and immunomodulatory mechanisms, therefore, its impact on intestinal barrier homeostasis deserves investigation.

**Aims:** To determine the efficacy of OA in the prevention of gut barrier alterations in EAE, with a focus on intestinal inflammatory- and oxidative-stress.

**Methods:** C57/BL6 mice were MOG35-55-immunized and treated with OA (25 mg/kg/day, i.p) or saline. On day 21, parameters related to i) oxidative stress (O<sub>2</sub><sup>-</sup> ions, lipid peroxidation), ii) inflammation (IL-1 $\beta$ , TNF $\alpha$ ) and iii) gut dysfunction (sCD14, intestinal fatty acid binding protein, I-FABP) were determined in serum and intestine. Studies related to intestinal permeability/structure were also performed.

**Results:** Histopathological analysis of colon and ileum showed high levels of O<sub>2</sub><sup>-</sup> ions (DHE stain), mucin loss (Alcian Blue/PAS stain) and an altered morphology (H&E stain), in untreated-EAE mice, whereas these effects were not detectable in tissues from healthy or OA-treated EAE mice. Intestinal permeability analysis showed an increase over 5-6 fold in EAE mice compared to healthy controls ( $p < 0.01$ ) that positively correlates with clinical symptoms, while in OA-treated EAE mice permeability only increased 2.5 fold ( $p < 0.01$ ). Accordingly, the expected high serum levels of sCD14 and I-FABP in EAE mice were prevented

by OA-treatment, only increased 1.2 and 1.3 times compared to controls ( $p > 0.05$ ). Similarly, OA intervention abolished lipid peroxidation, and the increased IL-1 $\beta$  and TNF $\alpha$  levels found in colon of EAE mice ( $2.7 \pm 0.4$  pg/mg tissue and  $1.2 \pm 0.7$  pg/mg tissue, respectively) were attenuated ( $1.1 \pm 0.5$  pg/mg tissue and  $0.5 \pm 0.1$  pg/mg tissue, respectively) in tissues of OA treated-EAE mice ( $p < 0.001$ ).

**Conclusion:** Our data contribute to the idea that intestinal dysfunction influences multiple sclerosis pathogenesis, and provides new findings regarding the beneficial activity of OA in EAE.

## Disclosure

Nothing to disclose

## EP1460

### Is DPP4/GLP-1 pathway a possible target for remyelination? - A first cerebellum-focused approach using the cuprizone mouse model

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**Introduction:** Cuprizone (CPZ) is a copper chelator that produces a reversible oligodendrocytopathy in animals, similar to human multiple sclerosis (MS). This model is attractive to study remyelination, but some of its fundamental properties are not yet fully characterized.

**Aims:** To deepen the knowledge about the biochemical profile associated with CPZ-induced demyelination and subsequent remyelination in the cerebellum, focusing on gliosis, inflammation markers and on the dipeptidyl-peptidase 4 (DPP4)/glucagon-like peptide-1 (GLP-1) pathway.

**Material and methods:** Two groups of male C57BL/6 mice ( $n=10$  each) were fed an oral solution of CPZ (0.2%) for 5 weeks (W5); half of the animals were subsequently kept under treatment with the vehicle (water) for another 2 weeks (W7). A vehicle-treated group was used as a control. After 5 and 7 weeks, the animals were subjected to gene expression and/or protein analysis studies of GFAP, myelin proteolipid protein (PLP), TNF- $\alpha$ , IL-1 $\beta$ , DPP4, GLP-1 and GLP-1R in the cerebellum, using techniques of RT-PCR, western blot and immunohistochemistry.

**Results:** Myelin PLP expression decreased in the cerebellum of CPZ-treated animals (W5), and these changes reverted at 7 weeks. GFAP levels varied in the opposite direction. The model also corroborated the existence of an underlying inflammatory process, revealed by the elevated expression of TNF- $\alpha$  and IL-1 $\beta$  in W5, normalizing in W7. Finally, the lack of changes in DPP4 and GLP-1 levels was accompanied by a reduction in GLP-1R levels in the cerebellum of W5 animals, as revealed by western blot.

**Conclusion:** The observed changes validate the use of W5 and W7 temporal moments for the study of demyelination and early remyelination in the cerebellum of these animals. The expression

profile of DPP4, GLP-1 and GLP-1R maintains intact the possibility of using this pathway as a possible therapeutic target in MS.

## Disclosure

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## EP1461

### NMO IgG and AQP4 peptide can induce aggravation of EAMG and immune mediated muscle weakness

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**Background:** Neuromyelitis optica (NMO) also known as Devic's disease is a central nervous system (CNS) autoimmune disease that preferentially affects the spinal cord and optic nerve. The disease is mediated by autoantibodies against Aquaporin 4 (AQP4). Myasthenia gravis (MG) is also an antibody-mediated disease that affects the neuromuscular junction, caused by autoantibodies against the nicotinic acetylcholine receptor (AChR) in 85% of patients. Recently increased prevalence of NMO was found in patients with MG and vice versa.

Currently the experimental autoimmune MG (EAMG) murine model is a good model for MG, but there is no good model for NMO.

**Aims:** To verify whether passive and active immunization with NMO-Ig and AQP4 peptides respectively, affect the severity and/or induce CNS pathology in EAMG.

**Methods:** We used EAMG induced in C57bl mice by immunization with Torpedo AChR and subjected the animals to passive transfer of NMO-IgG or to immunization with AQP4-derived peptide.

**Results:** Injection of either AQP4 peptide or NMO-Ig to EAMG or to naïve mice caused increased fatigability and aggravation of EAMG symptoms as expressed by augmented muscle weakness (but not paralysis), decremental response to repetitive nerve stimulation, increased neuromuscular jitter, and aberration of immune responses.

**Conclusions:** Increased disease severity in EAMG mice following immunization with the NMO autoantigen AQP4 or by NMO-Ig mediated by augmented inflammatory response can explain the clinical observation of increased susceptibility of patients with one autoimmune disease to develop a second autoimmune syndrome. Those models can serve as a tool to advance our understanding of how autoimmunity progresses and could help tailor therapy for those patients.

## Disclosure

Brill L: nothing to disclose  
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 Brenner T: nothing to disclose  
 Vaknin Dembinsky A: nothing to disclose

#### EP1462

##### **Innate immune activation is at the root of NMO-like lesion development**

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Neuromyelitis optica (NMO) is a heterogeneous condition with the histopathological hallmarks inflammation, demyelination and focal loss of aquaporin 4 (AQP4). While antibodies targeting AQP4 are believed to be central to NMO pathogenicity, anti-AQP4 immunoglobulin is absent in approximately one-fourth of NMO patients. Two distinct pathological entities might mediate tissue damage in NMO: innate and adaptive inflammation. We assume that innate and adaptive immunity cascades differentially regulate AQP4, and specifically contribute to the development of destructive NMO lesions. Innate inflammation was triggered by feeding young mice with 0.25% Cuprizone (Cup) mixed into ground rodent chow for 5 weeks. The liaison of innate and adaptive immunity was realized by combining the cuprizone model with active Experimental Autoimmune Encephalomyelitis (i.e. Cup/EAE). AQP4 distribution was further characterized in post mortem samples of progressive MS patients. ELISA was performed to screen for anti-AQP4 antibodies in our model. Discrimination of microglia and recruited monocytes was done using CX3CR1<sup>+/eGFP</sup> CCR2<sup>+/RFP</sup> mice.

Activation of innate immunity by cuprizone resulted in a pronounced diffuse AQP4 deposition within the demyelinated white matter. The same staining pattern was found in lesions of progressive MS patients. In the grey matter cortex, polarized AQP4 expression on astrocytic foot processes was lost, paralleled by a modest increase of diffuse staining intensity. Such lesions were characterized by reactive gliosis and pronounced microglia activation, but absence of T-cells and granulocytes. In Cup/EAE mice, several perivascular inflammatory infiltrates were found, and these were intensively populated by CCR2<sup>+</sup> monocytes, CD4<sup>+</sup> T-cells and granulocytes. Interestingly, anti-AQP4 staining intensity dramatically reduced at the close vicinity of perivascular infiltrates. Furthermore, some of these lesions showed retraction of perivascular astrocyte processes. These pathological changes occurred despite the absence of anti-AQP4 antibodies or focal complement deposition.

This study highlights the simultaneous effects of innate and adaptive immunity on AQP4 pathology. We propose that tissue damage in seronegative NMO patients begins with innate immune activation followed by secondary peripheral immune cell recruitment. The relation to types 4-6 lesions (Misu, Lassmann, Acta Neuropathol. 2013) remains to be clarified.

#### **Disclosure**

Sven Olaf Rohr: Nothing to disclose.  
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 Markus Kipp: Nothing to disclose.

#### EP1463

##### **Gender features of hyperprolactinemia as a protective factor in animal models of multiple sclerosis**

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Multiple sclerosis (MS) is a demyelinating disease which possesses significant gender differences: mostly progressive type in males and relapsing in females. Pregnancy alters the course of MS, which is presumably connected to the surge in prolactin secretion during 3 trimester. This makes prolactin a potential therapeutic agent and calls for further research. Cuprizone demyelination is one of the most relevant models of MS, as it mimics the progressive type of MS in mice. Prolonged cuprizone intoxication causes chronic demyelination with axonal degeneration, the main reason for permanent neurological damage.

This study was performed to estimate the protective role of drug-induced hyperprolactinemia in functional disability and morphological features of cuprizone demyelination in both male and female mice. The experiment featured mice strain C57BL/6 with 0,03 % cuprizone solution replacing drinking water for 12 weeks. Hyperprolactinemia was induced by subcutaneous injections of 125 µg metoclopramide, a widely-known dopamine-receptor antagonist, every two days. Control mice received saline injections on the same schedule. Central nervous system disabilities were evaluated with functional tests. The tests featured modified open field test (Tru Scan, Coulbourn Instruments) to evaluate general locomotor activity and anxiety, rotarod test for motor coordination, hot plate test for pain sensitivity and Noldus CatWalk for gait evaluation. Morphological analysis was performed with semi-thin sections for optical microscopy and ultra-thin sections for transmission electron microscopy with demyelinated and degenerated axons as morphometrical criteria.

It was shown that cuprizone intoxication causes more severe morphological CNS features than functional features. Furthermore the females are more susceptible to the demyelination, but the remyelination is more effective among females than males. Drug-induced hyperprolactinemia resulted in less severe CNS damage in both males and females on 6 and 12 weeks, but females featured much more efficient remyelination which is almost identical to the intact control group. Hyperprolactinemia has also shown almost identical and significant axonal degeneration reduction in both males and females. Therefore, prolactin shows a significant protective effect in both males and females by reducing demyelination and axonal degeneration lesions and requires further research as a potential therapeutic agent in multiple sclerosis.

#### **Disclosure**

Nothing to disclose

#### EP1464

##### **Antinociceptive effects of a chronic fingolimod treatment in an optimized recurrent-remittent experimental autoimmune encephalomyelitis mouse model of multiple sclerosis-neuropathic pain**

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**Background and aims:** Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system that causes different debilitating symptoms including neuropathic pain in many patients (47%)<sup>1</sup>. Among current treatments, fingolimod, a non-selective sphingosine-1-phosphate (S1P) receptor modulator showed promising effect on MS outcome. In the same time, the S1P pathway emerged as a novel therapeutic target for neuropathic pain<sup>2</sup>. While the antinociceptive effects of fingolimod have already been demonstrated in neuropathic pain<sup>3</sup> models no study have investigated this effect in an MS model. So our aim was to characterize the fingolimod effect in a relapsing-remitting (RR) experimental autoimmune encephalomyelitis (EAE) mouse model with neuropathic pain symptoms<sup>4</sup>.

**Methods:** We evaluated the effects of an early curative fingolimod treatment (0.5mg/kg/day) on clinical scores, motor performances as well as paw sensitivity to mechanical and thermal (cold and heat) stimuli.

**Results:** We showed in treated EAE mice that fingolimod: significantly ameliorates the clinical symptoms, totally reverses the mechanical allodynia and partially improves cold allodynia and thermal heat hypersensitivity.

**Conclusion:** We then showed for the first time that fingolimod can not only improves the EAE clinical scores but also ameliorates nociceptive symptoms. Given that neuropathic pain is lacking of efficient treatment, fingolimod could represent a first-line therapy in this subtype of MS patients.

**Perspectives:** We have to decipher if the fingolimod effects on nociceptive symptoms is dependent or independent to its effect on EAE score. In such a way we will evaluate the effect of sub chronic, late curative or local (i.e. intrathecal) treatment on both symptoms, as well as, characterize the cellular changes associated with these clinical improvements.

<sup>1</sup> *Foley et al., Pain 2014*

<sup>2</sup> *Welch et al., Biochem. Pharmacol. 2012*

<sup>3</sup> *Janes et al., Journal of Biological Chemistry 2014,*

<sup>4</sup> *Khan et al., Pharmacology, Biochemistry and Behavior 2014*

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Démosthènes: nothing to disclose.

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Bégou: nothing to disclose.

## EP1465

### Autoimmune and toxic demyelination is affected by HSP70 overexpression in oligodendrocytes and astrocytes

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Heat shock protein (HSP) are conservative proteins involved in proper protein folding, stress-induced cell responses, facilitating autoimmune response and neuroprotection. The role of HSP,

which are overexpressed in demyelinating lesion in MS brain, is unknown.

To examine HSP function in autoimmune (experimental autoimmune encephalomyelitis- EAE model) and toxic (lyssolecithine-LL injury) demyelination we produce transgenic mice with HSP70 overexpression specifically in astrocytes (GFAP/hsp70Tg) or oligodendrocytes (MBP/hsp70Tg). The MBP/hsp70Tg and GFAP/hsp70Tg mice were sensitized for EAE with myelin oligodendrocyte glycoprotein (MOG) peptide 35-55 and EAE was clinically scored to 1-5 grade scale. The remyelination processes were assessed after toxic demyelination induced by injection of LL into thoracic spinal cord. The remyelination in LL model of demyelination was assessed with toluidin blue staining.

The MBP/hsp70Tg mice showed enhance EAE symptoms in compare to control mice (2,5 v. 1,5, respectively). In LL model of demyelination enhanced damage of tissue and almost complete lack of remyelination was observed in MBP/hsp70Tg mice in compare to control mice (remyelination rank: 2,5 v. 7,8, respectively). These data suggest that hsp70 overexpression did not prevent oligodendrocyte demise but enhance inflammatory responses. Confirming this hypothesis was the observation that oligodendrocytes isolated from MBP/hsp70Tg mice were not resistant to TNF-induced death and lymphocytes isolated from EAE MBP/hsp70Tg mice showed enhance response to myelin antigen in compare to control mice (SI: 5,6 v. 2,2). In GFAP/hsp70Tg mice EAE symptoms were milder in compare to control mice (0,8 v. 1,5, respectively). The lymphocyte proliferation in response to myelin antigens were similar in GFAP/hsp70Tg and control mice. However the remyelination in GFAP/hsp70Tg mice after LL injection was slightly inhibited in compare to control mice as assessed by remyelination rank (6,1 v. 7,8, respectively). The hsp70 overexpression in oligodendrocytes did not change oligodendrocytes resistance to inflammatory-induced death but enhanced EAE symptoms and inflammatory responses. The hsp70 overexpression in astrocyte have protective effect on EAE course however do not enhance remyelination.

## Disclosure

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K. Selmaj nothing to disclose

## EP1466

### Inhibition of bone morphogenetic protein signaling with small molecules as a therapeutic approach in experimental autoimmune encephalomyelitis

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**Background:** Bone morphogenetic proteins (BMPs) are secreted proteins that belong to the TGF-beta superfamily. In the adult brain, BMPs modulate neurogenesis, favour astroglialogenesis and inhibit oligodendrogenesis, and they are also involved in demyelination

processes. Moreover, BMPs have been proposed as regulators of the immune response.

**Objective:** We aimed to test the therapeutic potential of two small molecules that inhibit BMP signaling (dorsomorphin and its analogue DMH1) in MOG-induced experimental autoimmune encephalomyelitis (EAE). Disclosure of conflict of interest: HE, LC-B, CC, GR-V, CE declare no competing financial interests. XM has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis, Teva Pharmaceuticals and Almirall.

**Methods:** EAE was induced in 8-week old C57BL6/J female mice with the 35-55 MOG peptide. Mice were randomized once EAE clinical signs were established, and animals were treated daily with 3mg/kg dorsomorphin (n=13), 5mg/kg DMH1 (n=13), or vehicle (DMSO; n=12). At the end of the experiment (day 29-33 postimmunization), we quantified inflammation and demyelination in the CNS. We evaluated the proliferative capacity of splenocytes upon antigen-specific (MOG<sub>35-55</sub>) or polyclonal (phytohemagglutinin or PHA) stimulus, and the frequency of peripheral immune populations (T cells, B cells and myeloid cells) by flow cytometry.

**Results:** Therapeutic treatment with dorsomorphin ameliorated EAE outcome measured as the area under the curve (AUC) of the mean daily clinical score for each group (vehicle group: 68.33±10.65 and dorsomorphin group: 54.52±19.27;  $p=0.039$ ). Treatment with DMH1 also resulted in a better EAE outcome (AUC: 52.65±18.34) compared with vehicle-treated mice ( $p=0.017$ ). Conversely, we did not find differences in the proliferative response of splenocytes upon stimulation with MOG<sub>35-55</sub> or PHA in vehicle-treated mice compared with dorsomorphin- and DMH1-treated groups. Because DMH1 is a more specific BMP-signaling inhibitor, we performed the histopathological study and the evaluation of the frequency of peripheral immune cells in DMH1-treated mice and vehicle-treated mice. DMH1-treated mice presented less inflammation in the CNS (inflammation score for vehicle group: 3.36±0.67, and for DMH1 group: 2.69±0.85;  $p=0.047$ ), and also presented a lower frequency of myeloid cells in the spleen (vehicle group: 70.86±6.72% and DMH1 group: 61.70±4.77%;  $p=0.015$ ). Moreover, macrophages were also decreased in the DMH1 group although no statistical significance was reached (vehicle group: 16.13±6.57% and DMH1 group: 10.11±3.34%;  $p=0.056$ ).

**Conclusion:** These data points to the specific inhibition of BMP signaling as a novel potential therapeutic target for MS.

## Disclosure

Founding source:

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## EP1467

### Functional regulation of *abcg2* by apolipoprotein E in context of immunotherapies for multiple sclerosis

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**Background:** The multi-drug resistance transporter ABCG2, a member of the ATP-binding cassette (ABC) family, mediates the efflux of different immunotherapeutics, e.g. teriflunomide (teri) and mitoxantrone (MX), across cell membranes and organelles. Functional relevance of ABCG2 on MX-treatment was demonstrated in MS and its animal model, experimental autoimmune encephalomyelitis (EAE), but data are lacking for teri.

Apolipoprotein E (apoE) is known to have modulatory effects on ABC-transporter activity as demonstrated in experimental stroke. We therefore hypothesize that *apoE* affects teri-efficacy via *abcg2*-modulation.

**Objective:** To investigate effects of *apoE*-deficiency on *abcg2*-transporter expression and its functional impact on teri-induced cellular effects *in vitro*.

**Methods:** *abcg2*-mRNA expression (spleen/splenic T cells and B cells) from wildtype (wt) and *apoE*<sup>-/-</sup>-mice were analyzed by qRT-PCR. Stimulated T cells from wt, *apoE*<sup>-/-</sup> and *abcg2*<sup>-/-</sup>-mice (anti-CD3, 10µg/ml + anti-CD28, 10ng/ml; 48h) were treated with teri (12.5-100µM). T cell apoptosis (annexinV/PI) and proliferation (CSFE) were analyzed by flow cytometry.

**Results:** We observed a 1.8-fold ( $p=0.003$ ) higher *abcg2*-mRNA expression in splenic T cells from *apoE*<sup>-/-</sup>-mice compared to wt, which was not present in B cells ( $p=ns$ ). Consistently, inhibition of T cell proliferation was 1.2-1.6-fold lower in *apoE*<sup>-/-</sup>-mice than in wt ( $p<0.05$ , 50-100µM teri, 48h). In line with the hypothesized effect of *abcg2* on teri-efficacy, T cells from *abcg2*<sup>-/-</sup>-mice revealed increased inhibitory effects of teri (1.3-1.9-fold increase compared to wt,  $p<0.05$ , 12.5-100µM teri, 48h). Teri-induced T cell apoptosis as independent functional readout demonstrated analogous results (*apoE*<sup>-/-</sup>: 1.2-fold decrease,  $p<0.01$ , 50µM teri and *abcg2*<sup>-/-</sup>: 1.2-fold increase,  $p<0.05$ , 12.5µM teri; each compared to wt).

**Conclusions:** Our data indicates that regulation of *abcg2*-expression by *apoE* has functional effects on cellular effects of teri. This ongoing work aims at contributing to an understanding of inter-individual differences in efficacy and adverse events of prominent ABCG2-transporter substrates such as teri.

## Disclosure

LS received travel grants from Genzyme. KG former employee of Biogen, not related to this work. RH received research and travel grants from Novartis and Biogen Idec. AS received speaker honoraria and/or travel compensation for activities with Almirall Hermal GmbH, Biogen, Merck, Novartis, Roche and Sanofi Genzyme, none related to this work. DMH received speaker honoraria and consulting fees from Servier. FL received research grants from Teva and Genzyme. AC has received personal compensation and research support from Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Roche, Teva and UCB in the last 3 years. All other authors report no disclosures. This study is supported by Genzyme.



## EP1468

**A new evaluation strategy to measure remyelination in the cuprizone model**

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**Background:** In multiple sclerosis (MS) patients, remyelination is pivotal for the maintenance of axonal integrity. While endogenous remyelination is robust in some patients, this regenerative process fails in others, especially during the progressive disease stage. One of the most popular animal models to test the pro-myelinating capacity of drugs is the cuprizone model. Effective drug testing requires, however, a detailed knowledge about regions where demyelination occurs in a reproducible and predictive manner.

**Objectives:** In this study, we aimed to define which part of the corpus callosum is consistently demyelinated and, thus, can serve as region of interest (ROI) to study remyelination.

**Method:** Acute demyelination was induced by a five week cuprizone (0.25%) intoxication protocol. Brain-slides were stained immunohistochemically for the mature myelin proteins PLP (proteolipid protein), MAG (myelin-associated glycoprotein) and CNPase (2',3'-cyclic nucleotide 3'-phosphodiesterase). Relative myelin densities were densitometrically analyzed within distinct sectors of the corpus callosum at the level of the anterior commissure and rostral hippocampus. Regions are given according to the Allen Brain reference Atlas (i.e. plate number).

**Results:** In all three stains, robust loss of immunoreactivity was observed within the corpus callosum. At the level of the anterior commissure (plate 54), demyelination of the midline of the corpus callosum was highly variable, irrespective which part was analyzed. At the level of the rostral hippocampus (plate 70), the extent of demyelination was relatively consistent within the most medial parts of the corpus callosum. At that level, the medial portion of the cingulum bundle served as a reliable landmark where demyelination becomes inconsistent.

**Conclusions:** This study clearly shows that reproducible demyelination can be obtained in the cuprizone model, allowing straight forward analyses of the pro-myelinating capacity of drugs. However, a pilot trial should be performed to define which region of the corpus callosum is demyelinated in a reproducible manner under the given experimental conditions.

**Disclosure**

Uta Chrzanowski: nothing to disclose

Markus Kipp: nothing to disclose

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## EP1469

**In vivo evolution by brain magnetic resonance imaging of interleukin 1 induced cortical demyelinating lesions in adult rats**B.A. Silva<sup>1,2</sup>, J.C. Avalos<sup>3</sup>, M.I. Fariás<sup>1</sup>, M.C. Leal<sup>1</sup>, C.H. Besada<sup>4</sup>, F.J. Pitossi<sup>1</sup>, C.C. Ferrari<sup>1,2</sup>*<sup>1</sup>Leloir Institute Foundation, <sup>2</sup>IUHI, Institute of Basic Science and Experimental Medicine, <sup>3</sup>Neurology Department, <sup>4</sup>Neuroimaging Department, Italian Hospital, Buenos Aires, Argentina*

The relevance of the interleukin 1beta (IL-1b) has been demonstrated in both Multiple Sclerosis (MS) pathology and MS animal models. The aim of this work is to analyze rat brain magnetic resonance imaging (MRI) and their correlation with the histological features of cortical demyelinating lesions induced by the long-term expression of IL-1b in adult rats. Adult rats were injected in prefrontal cortex with an adenovirus expressing IL-1b (AdIL-1). Then, 21 days after they were peripherally injected with either AdIL-1 or control adenovirus (CI/PI and CI/PC, respectively) and analyzed by 3 T MRI and histological techniques 7 days after the peripheral stimulation. Anatomopathological studies and brain blood barrier (BBB) integrity were assessed. The peripherally stimulated cortical lesions of CI/PI showed hyperintensity on T2-weighted sequence and homogeneous enhancement on T1-weighted sequence, after injection of a gadolinium-based contrast agent, with maximum enhancement six minutes after gadolinium injection, indicating lack of blood-brain barrier. We do not observed hyperintensity and gadolinium enhancement in cortical lesions of CI/PC animals. In spite of that, cortical lesions exhibited neuroinflammation, neurodegeneration, demyelination, meningeal inflammation and BBB disruption in both groups CI/PI and CI/PC. We analyzed the differences in the composition of both cortical lesions, and we found that the presence of neutrophils is significantly higher in CI/PI cortex, which could be responsible for MRI visualization on T2-weighted sequence. Given that no MRI lesion images can be visualized in CI/PC animals, even though tissue damage and BBB leakage is present, the phenomenon describes as normal appearing gray matter could explain these results. In addition, this study constitutes another evidence confirming that the low sensitivity of gadolinium in reflecting BBB disruption. Therefore, the use of conventional MRI protocols and the sensitivity of gadolinium to demonstrate BBB integrity should be discussed.

**Disclosure**

There are no conflicts of interest of the authors for this work

**Genetics/Epigenetics**

## EP1470

**Dimethyl fumarate changes the methylation pattern in CD4+ cells of MS patients**J. Lechner-Scott<sup>1,2,3</sup>, V.E. Maltby<sup>4</sup>, K.A. Ribbons<sup>1</sup>, M. Min<sup>1</sup>, R. Lea<sup>2</sup>*<sup>1</sup>Neurology, John Hunter Hospital, <sup>2</sup>Hunter Medical Research Institute, <sup>3</sup>Medicine and Public Health, <sup>4</sup>Health and Medicine, University of Newcastle, Newcastle, NSW, Australia*

**Background and aims:** The mode of action of the MS disease modifying therapy Dimethyl fumarate (DMF) is thought to be via the nuclear factor-like 2 pathway, leading to transcription of anti-inflammatory and cytoprotective genes. We have recently described significant differences in the methylation profile of CD4<sup>+</sup> T-cells of MS patients compared to age and gender-matched controls. In this study we explored if DMF can change the CD4<sup>+</sup> T-cell methylation profile.

**Methods:** Peripheral Blood Mononuclear Cells (PBMCs) were isolated by density gradient centrifugation on lymphoprep, and

CD4<sup>+</sup> T-cells enriched using EasySep magnetic negative selection from 7 relapsing remitting MS patients before and 6 months after treatment with DMF. Change in methylation was calculated using paired Tests. Point-wise FDRs and magnitude of change was used to rank CpGs. DNA was bisulfite converted and hybridized to Illumina EPIC methylation arrays and analysed as previously described (Graves et al 2013). Data was background corrected and control-normalized aligned to the human genome using BOWTIE. Methylation levels were produced from each probe and ranged from 0 (completely unmethylated) to 1 (completely methylated). Change in methylation was calculated by subtracting the median values of group 1 to group 2 to produce scores ranging from -1 (hypomethylation) to 1 (hypermethylation).

**Results:** We included 3 males and 4 females with a mean age of 35 years, 3 of which were treatment naïve. Mean disease duration was 2.8 years, mean EDSS 2.1 and an annual relapse rate of 1.1 prior to treatment. In total 1347 CpGs showed a change in methylation over time (FDR < 0.05) with 97% showing an increase in methylation, while only 3% showed a decrease. 216 CpGs had a larger than 10% difference in methylation. Most methylated regions were in known genes. GSEA-KEGG of the 1347 CpGs showed pathways involved in Wnt-signalling, axon guidance, focal adhesion and MAPK enriched. In particular tumour necrosis factor (*TNF*) on chromosome 6 showed increased methylation associated with DMF treatment. This is in contrast to our previous study where we demonstrated that this gene was significantly hypomethylated in MS patients compared to controls.

**Conclusion:** This study suggests that DMF potentially alters the methylation profile of CD4<sup>+</sup> T-cells in MS patients. We have previously shown that *TNF* is differentially methylated in MS patients compared to healthy individuals. This effect might to be corrected by DMF treatment.

## Disclosure

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## EP1471

### Occurrence of allele T of glypican 5 polymorphism is associated with sex and age at onset in multiple sclerosis patients

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**Introduction:** GPC5 gene has been implicated in multiple sclerosis (MS) susceptibility polymorphism studies as well as in the

pharmacogenomic GWAS (genome wide association study). It codes a glypican, a type of heparan sulfate proteoglycan that fulfills signaling functions in the extracellular matrix. Although, its exact mechanisms of action are still unknown, glypicans have been shown to contribute to neuronal development and function. A follow-up study successfully confirmed the connection between GPC5 single nucleotide polymorphisms (SNPs) and IFN- $\beta$  responsiveness. The aim of our study was to determine the association of selected polymorphisms of GPC5 gene with the treatment approach of our MS patients.

**Material:** The study group consisted of 174 patients (50 males and 124 females, age from 19 to 61.), who were sequentially recruited from the neurology outpatient clinic of Clinical Hospital in Białystok. All of them were relapsing-remitting MS patients undergoing immunomodulatory treatment, with EDSS ranging from 0 to 4,5.

**Description of methods:** The study was based on DNA analysis, that was extracted from the peripheral blood leukocytes using a classical salting out method. The SNP rs10492503 in the GPC5 gene were genotyped by TaqMan SNP genotyping assay using the real-time PCR method.

**Results and conclusion:** A strict correlation between the occurrence of allele T of rs10492503 polymorphism of GPC5 gene and sex and age of onset in MS patients was observed in our study. The male patients in the studied group with allele T were diagnosed earlier than female patients with the same allele ( $28 \pm 0.94$  vs.  $34.4 \pm 0.84$ ,  $p < 0.01$ ) and both, female and male patients with ancestral allele A ( $p < 0.01$ ,  $p < 0.05$ ). No significant association was found between clinical characteristics like scheme of treatment and EDSS scale changes. This result suggests, that the allele T of rs10492503 GPC5 gene can be a strong predictor of early-onset MS in male patients.

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## EP1473

### Single nucleotide polymorphism in vitamin D hydroxylase gene is associated with susceptibility to multiple sclerosis in Slovaks

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**Background:** Vitamin D has a large scale of immunomodulatory and antiinflammatory effects and it has been found to be involved in modulation of the risk and clinical course of multiple sclerosis (MS). The production of active form of vitamin D (calcitriol) is catalysed by 25-hydroxyvitamin D-1 $\alpha$ -hydroxylase, also known as CYP27B1. It is still not completely clear, whether the single nucleotide polymorphisms in *CYP27B1* gene could be related to the biological effects of vitamin D and thus to MS pathogenesis.

**Objectives:** The aim of our present study was to assess the association of the allele and genotype variants of rs703842 (C/T) in *CYP27B1* gene with the risk of MS development in Slovaks.

**Methods:** In our study, genotypes of rs703842 in *CYP27B1* gene were analysed in the group of 261 MS patients (87,4 % relapsing-remitting, 12,6 % secondary progressive) and 291 healthy age and sex-matched control subjects from central and northern Slovakia. Genotyping was performed by the polymerase chain reaction and restriction analysis.

**Results:** The allele T was found to be present in higher frequency in MS patients when compared to healthy controls (0.715 vs. 0.637,  $p < 0.01$ ). We also detected a significantly higher frequency of genotype TT in MS patients when compared to controls (0.513 vs 0.436,  $p < 0.01$ ).

**Conclusions:** We identified an increased frequency of minor allele T and genotype TT of rs703842 in *CYP27B1* gene in a cohort MS patients of Central European Slovak origin. The results of our study confirmed the role of rs703842 in MS pathogenesis, suggesting the allele T and genotype TT to be the genetic risk factors of MS development in Slovaks. Our findings support the hypothesis of genetic regulation of vitamin D effects in MS disease.

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## EP1475

### Cell-specific transcriptional modulation induced by fingolimod treatment in relapsing remitting multiple sclerosis patients

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**Background:** Fingolimod (FTY) is a second-line drug approved for Relapsing Remitting Multiple Sclerosis (RRMS). It is known

to prevent lymphocyte egress outside lymph nodes, thus reducing peripheral lymphocytes counts.

**Aims:** To investigate transcriptional changes induced by FTY in immune cell subtypes using RNA-seq technology, in order to better elucidate FTY mechanism of action at the molecular and pathway level.

**Methods:** 24 RRMS patients were sampled at baseline and after 6 months of FTY treatment. CD3+

T cells, CD20+ B cells and CD 14+ monocytes were sorted through the MACS MicroBeads system. RNA sequencing was performed on the three cell types using the Illumina TruSeq-Stranded mRNA preparation kit, on the NextSeq500 platform. Differentially expressed genes (DEGs) were identified for each cell type using DESeq2 R package. Genes strongly modulated by FTY (fold change [FC]>2 or

FC<0.5 and false discovery rate [FDR]<5%) were considered for a pathway enrichment analysis performed using WebGestalt tool, based on KEGG and Reactome databases.

**Results:** A marked up-regulation was observed in both T and B lymphocytes (695 up- and 492 down-regulated genes in T cells; 857 up- and 261 down-regulated genes in B cells), with evidence of significant overlap between the 2 cell-types; a less pronounced transcriptional induction was observed in monocytes, mainly regarding down-regulated genes (n=189). Most of FTY-responsive genes had immune-related function; among the top 10 DEGs, *CCL4* was up-regulated in T cells (adjusted p-value [adjp]= $5.4 \times 10^{-55}$ , FC=4.5), *FCGR3A* in B cells (adjp= $1.4 \times 10^{-31}$ , FC=5), whereas *CCR7* was down-regulated in monocytes (adjp= $3.1 \times 10^{-30}$ , FC=0.2). Up-regulated DEGs from T and B cells were enriched of genes involved in shared immune-related pathways (e.g. cytokine-cytokine receptor interaction, chemokine signaling pathways); similarly, also down-regulated genes in monocytes seemed to be involved in immune modulation (e.g. Th1 and Th2 cell differentiation pathways).

**Conclusions:** FTY induces major transcriptional changes at the immune level, that appear to be shared between T and B lymphocytes, whereas the induced gene expression modulation in monocytes is quite different. Our data suggest that at least part of the immunomodulatory action of FTY seems to be regulated at the transcriptional level.

## Disclosure

L. Ferrè, F. Clarelli, P. Provero, E. Mascia, G. Sferruzza and M. Sorosina report no disclosures.

L. Moiola received honoraria for speaking at meetings or for attending to advisory board from Sanofi-Genzyme, Biogen-Idec, Novartis and TEVA.

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G. Comi has received compensation for consulting services with the following companies: Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, Roche, Almirall, Chugai, Receptos, Forward Pharma and compensation for speaking activities from Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, Roche.

F. Martinelli Boneschi has received compensation for activities with Teva Neuroscience, Biogen Idec, Merck Serono as speaker and/or advisor.



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#### EP1476

##### Familial involvement in multiple sclerosis

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**Introduction:** Multiple sclerosis (MS) is defined as a chronic, inflammatory, and demyelinating disease of the central nervous system. MS is more frequently diagnosed in women and in individuals aged between 20 and 40 years. MS is an autoimmune disease caused by genetic and environmental factors that may be accompanied by other autoimmune diseases. Among our patients, 177 (11.2%) had a history of MS in other members of the family. The incidence of MS in the families of MS patients is 5%-26%.

**Results and conclusion:** Based on the data obtained from hospitals, 1,787 patients were determined to be living in the Middle Black Sea Region and were diagnosed with MS. The clinical and radiological diagnoses of MS of 1,584 patients were confirmed, whereas the diagnoses of MS in 203 were withdrawn. The prevalence of MS in Samsun province was 46.5/100,000. It was 43.2/100,000 in the Middle Black Sea Region, which was calculated based on the total population and total number of patients in the provinces and districts (Table 1).

The mean  $\pm$  standard deviation age of the patients was 38.2 $\pm$ 10.9 years; 1,121 (70.8%) patients were females, while 463 (29.2%) were males. The mean age at disease onset was 29.3 $\pm$ 7.6 years, with a mean age at disease onset of 29.33 $\pm$ 7.5 years in females and 29.53 $\pm$ 7.9 years in males.

A history of MS in other family members of patients was present in 177 (11.2%) patients. MS occurred in the sisters of 25 (14.1%) patients, mothers of 22 (12.4%) patients, brothers of 19 (10.7%) patients, daughters of 10 (5.7%) patients, fathers of 8 (4.5%) patients, and other relatives of 93 (52.5%) patients.

In the present study, familial MS was observed most often in second- and third-degree relatives. Among first-degree relatives, the frequency of familial MS was the highest in sisters, followed by mothers, brothers, daughters, and fathers. Although a higher frequency of familial MS in sisters and mothers is explained by the higher frequency of MS in women, some studies have reported a high rate of maternal inheritance of MS. A higher inheritance rate of familial MS in sisters than in mothers might be related to environmental factors. This can be explained by the fact that sisters and brothers are exposed to the same environmental factors during their childhood. The high frequency of familial MS in brothers in the present study might also support this opinion

#### Disclosure

nothing to disclose

#### EP1477

##### Role of CYP2R1 rs10766197 in MS risk and disease progression

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**Background:** Multiple sclerosis (MS) is a neurodegenerative autoimmune disease resulting from a complex interaction of genetic and environmental factors. Among these, vitamin D and genetic variants associated with vitamin D-metabolism gain great attention from scientific community.

**Objectives:** The aim of our study was to assess the role of NADSYN1 and CYP2R1 genes in relation to serum 25-OH-vitamin D3 levels in MS.

**Materials and methods:** We investigated on five single nucleotide polymorphisms in NADSYN1 and CYP2R1 genes in relation to serum 25-OH-vitamin D3 levels in 105 MS patients and 130 controls. Genotyping of CYP2R1- and NADSYN1-SNPs was performed by TaqMan allelic discrimination (Life Technologies).

**Results:** We found lower 25-OH-vitamin D3 concentrations in MS patients than in controls. The most relevant finding obtained allows us to propose that rs10766197 CYP2R1 SNP is associated with MS risk. After stratifying MS patients according to gender, we found that the minor allele A of rs10766197 had a higher frequency in men in comparison to women affected by MS and an association with disease progression, assessed by EDSS and MSSS scores, only in MS men.

**Conclusions:** This finding opens new perspectives for a role of CYP2R1 in both risk and progression of MS.

#### Disclosure

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Concetta Scazzone, Luisa Agnello, Bruna Lo Sasso, Chiara Bellia, Giulia Bivona, Rosaria Schillaci, and, Marcello Ciaccio have nothing to declare.

#### EP1478

##### Association between DRB1\*15:01 allele and five distinct Single Nucleotide Polymorphisms in the Brazilian familial form of multiple sclerosis

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**Background:** Considerable epidemiological and laboratory data have shown that Multiple sclerosis (MS) results from a complex interaction between genetic and environmental factors. To better understand the mechanisms among the genetic variations and susceptibility to the disease, the familial form of MS (ffMS) are being studied.

**Objective:** To investigate, regarding susceptibility to MS, the association between HLA type II allele and five different Single Nucleotide Polymorphisms (SNPs) in genes Interleukin 7 receptor

alpha (IL7Ra), Estrogen receptor (ESR), Vitamin D receptor (VDR) and CIITA.

**Methods:** A case-control study was conducted with a miscigenated sample of 29 Brazilian familial MS patients (22 females and 7 males, 26 of whom were white, and 3 were black) from referral centers in Rio de Janeiro-Brazil, and 296 free disease controls (200 females and 96 males). DRB1\*15:01 allele and SNPs in genes IL7Ra (rs6897932), VDR (rs731236), ESR (rs1033182) and CIITA (rs3087456; rs4774) were assessed by techniques of PCR, electrophoresis and DNA sequencing. In the association analysis, it was used Qui-square test.

**Results:** DRB1\*15:01 allele was significantly more frequent in Familial MS patients (62% vs. 7.4%,  $p < 0.001$ ). In addition, all studied SNPs were more frequent in the free disease group (rs6897932 IL7Ra: 27.5% vs. 32%,  $p = 0.61$ ; rs731236 VDR: 27.5% vs. 55%,  $p = 0.004$ ; rs1033182 ESR: 31.8% vs. 50.6 %,  $p = 0.006$ ; rs3087456 CIITA: 17.2% vs. 44.2%,  $p = 0.004$ ; rs4774 CIITA: 7.4% vs. 43.2%,  $p = 0.0001$ ), which shows a tendency of non-association with ffMS, in the miscigenated Brazilian sample of patients.

Moreover, in these patients with Familial MS, no association was found between the presence or not of HLA DRB1 15\*01 allele and frequency of SNPs rs6897932 IL7Ra (33% vs. 18.1%,  $p = 0.37$ ), rs731236 VDR (33% vs. 18.1%,  $p = 0.375$ ), rs1033182 ESR (22.2% vs. 27.2%,  $p = 0.757$ ), rs4774 CIITA (11% vs. 9%,  $p = 0.86$ ), and rs3087456 CIITA (11% vs. 27.2%,  $p = 0.263$ ).

**Conclusion:** A strong association between ffMS and the presence of the DRB1 15\*01 allele was evidenced, suggesting that, in a miscigenated population such as Brazil, this is the most related factor with disease susceptibility, more than the studied SNPs.

No association between those SNPs and disease was found in the small sample of ffMS patients. Therefore, more studies with a larger sample should be implemented.

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## Immunology

### EP1479

#### Modulation of the Treg: Th17 axis in relapsing remitting multiple sclerosis after dimethyl fumarate therapy

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Dimethyl fumarate (DMF) is a disease modifying therapy licensed as a first line therapy for relapsing remitting multiple sclerosis (RRMS). The exact mechanism of action of DMF is not clear, although it has been proposed to exert both anti-inflammatory and antioxidant effects on immune cells, and to cause apoptosis in T

cells. Pro-inflammatory T cells such as Th1 and Th17 cells are proposed to have a pathogenic role in MS, whereas regulatory T (Treg) cells suppress pathogenic T cells and prevent autoimmunity. We examined the immunomodulatory effects of DMF treatment in RRMS patients, comparing baseline, 1, 3 and 6 months post treatment. We used multi-parameter flow cytometry to determine the frequency and phenotype of peripheral CD4 T cells. Preliminary data indicated a significant reduction in the frequency and absolute numbers of memory CD4 T cells, with a corresponding increase in the naïve compartment after 6 months of treatment. Pro-inflammatory cytokines IL-17, IFN- $\gamma$ , TNF, GM-CSF production by CD4 T cells was not altered by DMF treatment, however there was a significant reduction in the expression of the CD161 Th17 lineage marker after 6 months. In addition we observed a significant increase in the frequency of IL-2 producing T cells after 3 and 6 months relative to baseline. There was a non-significant trend towards an increase in Treg cells in response to DMF treatment, however the proportion of memory Treg cells was significantly reduced after 6 months.

In summary, DMF therapy appears to specifically target memory CD4 T cells within both the effector and Treg compartments, resulting in a reciprocal increase in the proportion of naïve CD4 T cells. The increase in IL-2 production may reflect a decrease in effector memory T cells which have a reduced capacity for IL-2 production. The reduction in CD161 expression in response to DMF therapy suggests that DMF may specifically target Th17 lineage cells, however no corresponding reduction in IL-17 cytokine was observed and increased patient numbers need to be analysed. Finally DMF therapy for 3 or 6 months significantly decreased the CD161+ Th17:Treg cell ratio suggesting that DMF therapy may in part exert its effects via reciprocal effects on Th17 and Treg cells.

## Disclosure

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### EP1480

#### IL-24 is produced both locally and peripherally by activated immune cells of MS patients

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**Background:** IL-24 is a cytokine of the IL-10 family and IL-20 subfamily. It shares receptor chains with IL-22 and IL-26, two cytokines which have shown to be associated with the IL-17 producing T helper (TH) subset TH17. It is well established that TH17 lymphocytes, as well as the cytokines they produce, are crucial in the pathogenesis of multiple sclerosis (MS). IL-24 has been shown to be elevated in patients with chronic inflammatory/auto-immune disorders such as rheumatoid arthritis, inflammatory bowel disease and psoriasis, however studies in MS are lacking. Here, we evaluate the unexplored role of IL-24 in MS.

**Methods and results:** Using quantitative PCR (qPCR), we show that IL-24 mRNA is expressed by activated T cells, B cells and monocytes of healthy donors (HD). In naive T cells, IL-24 mRNA is specifically induced by the combination of IL-6 and TGF- $\beta$ . Memory T cells, after differentiation into either TH1 or TH17 cells, express both IL-24 mRNA and protein, as assessed by qPCR and ELISA respectively, in HD and MS patients. Interestingly, the concentration of IL-24 is significantly higher in plasma samples of MS patients, compared to HD, as measured by ELISA. In our study cohort, immunomodulatory treatment significantly reduced the concentration of IL-24 in plasma samples. Using immunohistochemistry on active MS lesions, we identified IL-24 expressing myelin-phagocytosing myeloid cells, as well as reactive astrocytes, which were both validated using *in vitro* cultures of primary human macrophages and astrocytes.

**Conclusions:** In summary, IL-24 is increased in the blood of MS patients, and it is expressed by activated lymphocytes, myelin-phagocytosing myeloid cells and reactive astrocytes in the context of neuroinflammation, warranting further investigation into its biological role in the context of MS.

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## EP1481

**Melanocortin receptor mediated anti-inflammatory effect of repository corticotropin injection on human monocyte-derived macrophages**

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**Introduction:** Repository corticotropin injection ((RCI), H.P. Acthar Gel®) contains a purified porcine pituitary ACTH-analogue and is FDA-approved to treat acute multiple sclerosis (MS) exacerbations. ACTH may have activity at all five melanocortin receptor (MCR) subtypes that are differentially expressed on multiple

immune and non-immune cell populations. MRC agonists are reported to inhibit pro-inflammatory responses in blood-derived macrophages. Monocyte-derived-macrophages (MDMs) are the dominant cell type in an MS lesion and play a pivotal role in regulating the immune response and development of plaques in MS.

**Objective:** To explore the direct effects of RCI on human macrophages *in vitro*, focusing on induction of pro-inflammatory mediators following lipopolysaccharide (LPS) stimulation.

**Methods:** Human blood derived monocytes were selected for CD14 expression using magnetic bead selection (MACs) and plated in presence of macrophage colony-stimulating factor (M-CSF). Cells were stimulated with LPS and incubated for a minimum for 24h with and without RCI preparations (3h pre-treatment). Assays: qPCR assays were performed using Taqman platform. ELISA reagents for various cytokines were sourced from BD Biosciences. Receptor expression data was mined from microarray and RNAseq datasets.

**Results:** MDMs express MC1R exclusively as shown by transcriptomic and PCR analysis. Expression of MC1R was reduced by LPS stimulation and this was not affected by RCI application. Treatment of MDMs with RCI suppressed LPS-induced production of TNF and IL6 (range, 75-80%). Furthermore, RCI treatment of MDMs induced expression of heme oxygenase-1 (HMOX1), a gene that is upregulated during periods of metabolic stress.

**Conclusion:** Our *in vitro* study showing that RCI directly inhibits the pro-inflammatory response of human MDMs indicates that this agent can induce an anti-inflammatory effect independent of the corticosteroid pathway. Whether this anti-inflammatory effect on MDMs can impact other functional roles such as phagocytosis, tissue repair or promoting remyelination remains to be established.

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## EP1482

**Differential gene expression of SMAD family members and SIPR1 in circulating CD4+ T cells in multiple sclerosis**

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**Background:** CD4+Th17 cells play a predominant role on T cell-mediated immunity on Multiple Sclerosis (MS). Previously, we showed that *SMAD7* and *SIPR1* were differentially regulated in relapsing-remitting MS (RRMS) patients versus healthy donors (HD). *SMAD* family mediates signalling of the TGF- $\beta$  pathway, related to Th1/Th17 shift in autoimmune CNS inflammation.



Sphingosine 1-phosphate regulates lymphocyte egress from lymphoid organs. To date, conflicting data about SMAD member's expression and *SIPRI* have been described in RRMS. In Crohn's disease (CD), another autoimmune condition, *SMAD7* is clearly upregulated in the gastrointestinal mucosa.

**Objectives:** To compare gene expression changes of SMAD members and *SIPRI* in RRMS, compared to CD patients and HD.

**Methods:** PBMCs were purified by gradient density from 20 ml of fresh blood. CD4<sup>+</sup> T lymphocytes were isolated by negative selection and magnetic separation. RNA was isolated from CD4<sup>+</sup> T cells and cDNA transcribed. *SMAD2*, *SMAD3*, *SMAD4*, *SMAD7* and *SIPRI* genes were quantified by qRT-PCR in 20 HD, 20 RRMS patients without disease activity, 40 RRMS patients during a relapse, and 20 CD patients on active relapse. False discovery rate corrected by Benjamini-Hochberg was calculated for comparisons between groups.

**Results:** Compared to HD, we found *SMAD7* and *SMAD3* were underexpressed in stable RRMS patients (-3.2x-fold and -1.4x-fold, respectively). *SMAD7* (-2.4x-fold), *SMAD4* (-1.2x-fold) and *SIPRI* (-1.4x-fold) were downregulated in RRMS patients during a relapse. Finally, all analyzed genes were downregulated in active CD patients (*SMAD7*, -4.8x-fold; *SMAD4*, -1.7x-fold; *SMAD3* -1.9x-fold; *SMAD2*, -1.3x-fold and *SIPRI*, -1.7x-fold).

**Conclusions:** Transcription of *SMAD* family members and *SIPRI* gene is lower in RRMS patients during both relapsing and remitting phases, and in active Crohn disease patients.

## Disclosure

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## EP1483

### Evaluation of neutrophil lymphocyte ratio in multiple sclerosis

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**Background:** Neutrophil-to-lymphocyte ratio (NLR) is usually considered as a simple and cost effective parameter to evaluate inflammatory status. Studies have shown high NLR values in cases of acute or chronic inflammation, such as acute pancreatitis, chronic tonsillitis, acute mesenteric ischaemia, coronary artery disease, heart failure, diabetes mellitus, psoriasis and other malignancies. There are very few studies examining the relationship between multiple sclerosis (MS) and NLR.

**Aims:** The aim of this study was to investigate NLR in patients with MS in relapse and during remission.

**Methods:** In this study we analyzed data of patients with a diagnosis of MS according to revised Mc Donald criteria who admitted to our hospital between September 2016 and April 2017. Patients who have infection, chronic diseases such as diabetes mellitus, hypertension, malignancy, liver disorders, kidney disorders, other autoimmune diseases and patients receiving Fingolimod, Dimethyl fumarate and Natalizumab treatment were excluded from the study. Blood samples were collected before treatment with intravenous corticosteroids in patients with relapse. Complete blood counts as well as demographic and clinical data from MS patients were evaluated.

**Results:** Ninety-nine MS patients (36 patients in relapse; 63 patients in remission) were included in the study. The neutrophil count was significantly higher in patients who were in relapse than in patients in remission ( $5.90 \pm 2.88 \times 10^9/L$  vs.  $4.24 \pm 1.54 \times 10^9/L$ ;  $p = 0.001$ ). Although lymphocyte count was found higher in patients during relapse than in patients in remission ( $2.36 \pm 1.11 \times 10^9/L$  vs.  $2.06 \pm 0.7 \times 10^9/L$ ) this difference was not statistically significant ( $p = 0.122$ ). NLR was significantly higher in patients with relapse than patients in remission ( $3.79 \pm 0.6$  vs.  $1.26 \pm 0.17$ ).

**Conclusions:** NLR may be a simple and inexpensive laboratory method to evaluate inflammation in MS patients but further prospective studies with the high number of patients and long follow-up time are needed.

## Disclosure

Azize Esra Gürsoy: Nothing to disclose

Zehra Cemre Renk: Nothing to disclose

Talip Asil: Nothing to disclose

## EP1484

### Multiple arboviral infections and the risk of development of neurological complications

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**Introduction:** There was a sharp increase of patients with peripheral nervous system (PNS) disorders such as Guillain-Barré Syndrome (GBS) and central nervous system (CNS) disorders after the outbreak of the arbovirus infections in Brazil. However, it is unclear which patient is at an increased risk to develop neurological complications after Zika (ZIKV), Chikungunya (CHIKV), and Dengue (DENV) infections.

**Objective:** To evaluate the seropositivity for ZIKV, CHIKV and DENV in patients with neurological complications after arboviruses infections, and assess antibodies against aquaporin-4 (AQP4) and myelin-oligodendrocyte glycoprotein (MOG).

**Methods:** We evaluated 35 patients from 2 centers in the Northeast of Brazil (Fortaleza and Recife) who presented with neuroimmunological disorders after arboviruses infection. We detected serum IgM and IgG antibodies against ZIKV, CHIKV, DENV using ELISA kits. Anti-AQP4 and anti-MOG were tested using the cell-based assay.

**Results:** Among the total of 35 patients, the majority ( $n = 21$ ) had PNS manifestations - nineteen (90.4%) had GBS and two patients (9.5%) developed chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Thirteen of 21 (61.9%) patients were positive for two viruses - 12/13 DENV+ZIKV and 1/13 DENV+CHIKV. Two of 21 (9%) patients were positive for all three viruses DENV+CHIKV+ZIKV. Six of 21 (28.6%) patients were positive only for DENV. The remaining 14/35 (40%) patients developed CNS complications (myelitis, encephalitis and optic neuritis). Eight of 14 (57%) patients had positivity for two or three viruses - 2/14 ZIKV+DENV, 3/14 CHIKV+DENV, 3/14

DENV+CHIKV+ZIKV. The remaining six patients were positive for one virus (5/14 DENV; 1/14 CHIKV). None of the patients had AQP4 antibodies and one patient was anti-MOG IgG positive (positive for ZIKV+DENV IgG).

**Conclusion:** Multiple viral infections may increase the risk of development of neurological complications. The development of autoantibodies such as anti-AQP4 and anti-MOG in those patients is rare.

### Disclosure

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Douglas Kazutoshi Sato: nothing to disclose.

### EP1485

#### Effect of serum of patients with optic neuromyelitis on the differentiation of neural stem cells. Preliminary study

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**Background:** Optic neuromyelitis (NMO) is an autoimmune, demyelinating, and neurodegenerative disease that primarily affects the optic nerve and spinal cord. AQP4-IgG (IgG-NMO), a specific autoantibody against aquaporin 4 channel is expressed in certain areas of the brain and some particular cells, such as astrocytes, has been linked to the etiopathogenesis of the disease. Our aim was to evaluate in vitro the effect of this immunoglobulin on the proliferation and differentiation capacity of neural progenitor cells in culture to elucidate the possible role of the antibody in the disease.

**Methods:** Serum samples from six patients diagnosed with NMO and seropositive for IgG-NMO and four healthy controls were used. Neurospheres were extracted from young BALB/c mice and cultured in complete medium (DMEM supplemented with hormone mix, trophic factors and 5% FBS), at passage 5 the neurospheres were divided into three groups and the culture media were supplemented with: 2% HC serum; 2% of patients serums with NMO and sham which only contained the culture medium; after 10 days of differentiation the neurospheres were fixed for later analysis by immunohistochemistry for the identification of Tuj1, GFAP and OLIG2.

**Results:** In the neurosphere cultures, alterations in the differentiation were observed, showing a lower rate of OLIG2 cells (Sham:  $20,22 \pm 3,2$ ; HC:  $21,6 \pm 2,4$ ; NMO:  $8,93 \pm 3,7$ ;  $P < 0.05$ ). Higher number of GFAP positive cells in patients with NMO compared to sham and HC (Sham:  $64,04 \pm 3,2$ ; HC:  $60,9 \pm 4,5$ ; NMO:  $80,82 \pm 2,5$ ;  $P < 0.05$ ) were observed. In the differentiation to the neuronal

strain only Tuj1 decrease was found (Sham:  $15,74 \pm 2,6$ ; HC:  $17,5 \pm 1,5$ ; NMO:  $10,82 \pm 3,3$ ;  $P < 0.05$ ).

**Conclusions:** The serum affects the proliferation and differentiation of the neurospheres in the different cell lineages, mainly compromising the number of neuronal cells and oligodendroglia.

### Disclosure

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Álvaro Gómez Graña: nothing to disclose  
Jordi Matías-Guiu Antem: nothing to disclose  
Inés González Suárez: nothing to disclose  
C. Oreja-Guevara: nothing to disclose  
Ulises Gómez Pinedo: nothing to disclose  
Jorge Matías-Guiu Guía: nothing to disclose

### EP1486

#### Cell mechanical phenotyping of peripheral blood leukocytes in multiple sclerosis patients

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**Background:** There is a growing interest on modulation of biophysical properties of immune cells. Cell deformation and mechanical phenotyping is of special interest as cytoskeletal alterations are supposed to be intimately connected with important cell function. The real-time deformability cytometry (RT-DC) is a novel method to characterize mechanical properties of cells. Previous reports presented how RT-DC can distinguish cell-cycle phases, stem cell differentiation and cell populations in whole blood by their mechanical fingerprints. It is discussed, that physiological and pathological changes could be reflected by mechanical phenotyping. Only few data are available regard mechanical phenotyping in immune cells and no studies are available in MS.

**Methods:** With RT-DC large populations of cells can be analyzed regard cytoskeletal alterations. Cells are flowed through a microfluidic channel constriction and deformed by shear stress and pressure gradients. First, deformation of different immune cell subtypes was evaluated. By in vitro analyses changes in deformation of different lymphocyte subtypes and antigen-presenting cells upon maturation and activation were investigated. Additionally, differences in cell mechanical properties between MS patients and healthy controls were evaluated. Impact of monoclonal-antibody therapies were assessed.

**Results:** There are distinct differences in deformation between lymphocytes and monocytes/granulocytes in investigated blood samples. Upon stimulation and maturation T cell subtypes presented increased deformation compared to immature state. Additional analyses over time as defined by time kinetic measurements presented selective changes in degree of deformation with development and selection of different subgroups defined by various degrees in deformation. There were distinct changes in deformation of peripheral immune cell subtypes directly after monoclonal-antibody application including natalizumab,

alemtuzumab and ocrelizumab treatment in MS patients. Impact on deformation differed between acute versus long-term effects during monoclonal antibody therapy.

**Conclusion:** Here we present distinct patterns of cell mechanical characteristics of different peripheral immune cell subtypes and its modulation during maturation and activation. First data indicate selective impact on cell mechanical properties during treatment. Further studies will elucidate how cell mechanical phenotyping can act as biomarker in clinical practice.

## Disclosure

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## EP1487

### Predictive biomarkers for optimal therapeutic response to fingolimod treatment in multiple sclerosis patients

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**Background:** Fingolimod (FTY720) is one of the first-line therapies for relapsing-remitting multiple sclerosis (RRMS), which sequesters T-cells to lymph nodes through functional antagonism of sphingosine-1-phosphate 1 receptor, thereby reducing the number of potential autoreactive cells migrating to the central nervous system.

**Objective:** To evaluate an extensive panel of leukocyte subpopulations in peripheral blood as potential biomarkers of therapeutic response to fingolimod.

**Methods:** Longitudinal analysis of T, B, NK, monocyte and dendritic-cell subpopulations was performed by multiparametric flow-cytometry in 45 RRMS patients at baseline and after +1, +3, +6 and +12 months of fingolimod treatment. Data were analyzed using Kolmogorov-Smirnov test. In case of no-normal distribution, Wilcoxon, U-Mann Whitney or Kruskal-Wallis test were used, as appropriate.

**Results:** Fingolimod treatment induced a severe lymphopenia affecting mainly T and B cells. However, an relative increase of Tregs (memoryTreg: baseline:  $3.8 \pm 1.0$  % vs month +1:  $8.8 \pm 4.4$  % and activatedTreg: baseline:  $1.5 \pm 0.7$  % vs month +1:  $3.7 \pm 2.1$  %,  $p < 0.001$ ) and transitional B- cells (baseline:  $10.5 \pm 12.3$  % vs month +1:  $18.7 \pm 14.6$  %,  $p < 0.001$ ) was observed. Interestingly, lymphocyte subpopulations were significantly different in responder patients already at baseline, highlighting a lower

percentage of Recent Thymic Emigrants (responder:  $4.0 \pm 1.4$  % vs non-responder:  $7.4 \pm 1.9$  %,  $p < 0.000$ ).

Patients that suffered clinical relapses during follow-up had higher percentage of CM CD4<sup>+</sup> (relapsed:  $36.1 \pm 8.8$  % vs non-relapsed:  $27.2 \pm 5.2$  %,  $p < 0.05$ ) as well as Th1Th17 (Th1Th17 TCM: relapsed:  $15.4 \pm 6.2$  % vs non-relapsed:  $10.5 \pm 4.1$  %,  $p < 0.05$ ) at baseline compared to relapse-free patients.

**Conclusions:** These results support that immune-monitoring of minor lymphocyte subpopulations in peripheral blood is a powerful tool for the management of patients under fingolimod treatment that may be extrapolable to other immunotherapies.

## Disclosure

Nothing to disclose

## EP1488

### Cerebrospinal fluid B-cell phenotype and intrathecal IgG synthesis suggest a local on-going follicular reaction in multiple sclerosis at clinical onset

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**Background:** Multiple sclerosis (MS) is characterized by multiple immunological dysfunctions that lead to the expansion of T and B autoreactive clones and to intrathecal anti-central nervous system (CNS) antibody production. Although cerebrospinal fluid (CSF) B cells are easily accessible and may reflect relevant immune-pathological events within meninges and brain parenchyma, they have been poorly studied so far.

**Aim:** To characterize CSF B-cell subsets at clinical onset in order to evaluate their diagnostic and prognostic value.

**Methods:** Paired CSF and serum samples were obtained from 17 patients (13 RRMS, 4 CIS) and 20 individuals affected by non-inflammatory neurological diseases (NIND). The intrathecal IgG synthesis was evaluated by means of quantitative formulae and the demonstration of IgG oligoclonal bands (IgGOB). B cell subsets in the CSF were analyzed by Flow-Cytometry and classified in naive B cell (CD19+CD20+CD27-), memory B-cells (CD19+CD27+), plasmablasts (PB, CD19+CD27++CD38++CD138-) and plasmacells (PC, CD19+CD27++CD38++CD138+).

**Results:** Mild CSF pleocytosis ( $8.9 \text{ cell}/\mu\text{l} \pm 6.9$ ) and detectable B-cells ( $2.0\% \pm 0.5$  of nucleated CD45<sup>+</sup> cells) were found in RRMS patients but not in NIND ( $1.1 \text{ cell}/\mu\text{l} \pm 0.8$ ) B cell ( $0.2 \pm 0.0$ ). Memory B cell significantly varied among patients ( $60.7\% \pm 20.3$  of CD19<sup>+</sup>), as well as PB ( $35.2 \pm 15.1$  of CD19<sup>+</sup>CD27<sup>+</sup>) and PC ( $64.1 \pm 14.7$  of CD19<sup>+</sup>CD27<sup>+</sup>). Of note, no PB or PC could be detected in CIS patient. A mild correlation was observed between whole B cell and quantitative indexes of intrathecal IgG synthesis ( $r: 0.6$ ,  $p < 0.05$  for both IgG Index and IgGIF). Further correlation analysis between quantitative indexes of intrathecal IgG synthesis and single B-cell subsets disclosed a strong correlation with PC ( $r: 0.89$ ,  $p < 0.05$  and  $r: 0.90$ ,  $p < 0.05$ , respectively), and a correlation trend, even if not statistically significant, with PB ( $r: 0.80$ ,  $p = 0.055$  and  $r: 0.68$ ,  $p = 0.137$ , respectively).

**Conclusions:** The correlation between CSF PC/PB and quantitative indexes of intrathecal IgG production supports an on-going



follicular reaction. Whether this phenomenon is intrathecally-exclusive or occurs in the periphery as well, will need coupled analysis of CSF and blood samples investigations. Even though preliminary, the absence of PB and PC in CSF of CIS patients could suggest a role of these subsets in the conversion to clinically defined MS. Larger population and long-term follow-up will help to evaluate their diagnostic and prognostic values in MS.

### Disclosure

Grassivaro F, Venturini M, Toffanin E and Ruggero S have nothing to disclose.

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Gallo Paolo has been a consultant for Bayer Schering, Biogen Idec, Genzyme, Merck Serono and Novartis; has received funding for travel and speaker honoraria from Merck-Serono, Biogen Idec, Sanofi-Aventis, Novartis Pharma and Bayer-Schering Pharma, Teva; has received research support from Bayer, Biogen Idec/Elan, MerckSerono, Genzyme and Teva; and has received research grant from the University of Padova, Veneto Region of Italy, the Italian Association for Multiple Sclerosis, the Italian Ministry of Public Health.

### EP1489

#### Disturbance of human brain endothelial barrier function via chemokine receptor CXCR2

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**Background:** Recruitment of myelin-reactive CD4<sup>+</sup> T cells to the CNS across the blood-brain barrier (BBB) is considered critical in the pathophysiology of multiple sclerosis (MS). There is emerging evidence, however, that also innate immune cells contribute to MS pathophysiology. Levels of the neutrophil-attracting chemokines CXCL5 and CXCL8 are elevated in plasma and cerebrospinal fluid of patients with MS and CXCL5 levels positively correlate with disease activity. Interestingly, CXCR2, a high affinity receptor for CXCL5 and CXCL8, is not only expressed on leucocytes, but also on non-hematopoietic cells including endothelium. This prompted us to evaluate the expression and function of CXCR2 in human brain endothelium.

**Methods and results:** Here we demonstrate that resting human brain endothelial cells (hCMEC/D3 cell line) express low levels of CXCR2. Both in response to inflammatory stimulation with TNF $\alpha$ , IL1 $\beta$  or TNF $\alpha$  + IFN $\gamma$  as well as after hypoxia (1% O<sub>2</sub>),

CXCR2 protein expression is up-regulated, as demonstrated by Western blot analysis. This is preceded by a corresponding increase in CXCR2 mRNA levels. For label-free real-time assessment of transendothelial resistance, cells were cultivated in an ACEA xCELLigence DP system, until they formed a confluent monolayer with tight junction formation, as indicated by a stable plateau of the cell index. Physiologically relevant, low nanomolar concentrations of recombinant CXCL5 and CXCL8 caused a dose-dependent and long-lasting decrease in transendothelial resistance of resting cells. This barrier-perturbing effect was further pronounced under inflammatory conditions and attenuated by pre-incubation with a specific CXCR2 inhibitor, suggesting a CXCR2-dependent mechanism.

**Conclusions:** CXCR2 is expressed on human brain endothelium and its expression is highly inducible by inflammatory stimuli or hypoxia. The neutrophil-attracting CXC chemokines CXCL5 and CXCL8 perturb barrier function of human brain endothelial cells via CXCR2. This mechanism may contribute to BBB breakdown and lesion formation in MS and represent a novel therapeutic target.

### Disclosure

Axel Haarmann, Michael Schuhmann, Guido Stoll and Mathias Buttmann have nothing to disclose.

### EP1490

#### Fractalkine (CX3CL1) in the sera of patients with multiple sclerosis and Neuro-Bechet's disease

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Chemokines are inducible cytokines. Priorly they known as a chemotactic factors, but now they considered in various conditions. Fractalkine (CX3CL1) is a unique chemokine that can exist in a soluble form, as a chemotactic cytokine, or in a membrane-attached form that acts as a binding molecule. It is constitutively expressed in central nervous system (CNS). Especially on neurons, endothelial cells, microglia. Microglia are the main representatives of the immune system in the healthy brain. Inflammation and neuronal damage cause to increase levels of this chemokine. CX3CL1 can reduce neuroinflammation and has a neuroprotective role in CNS by reducing neurotoxicity and microglial activation.

The objective of this study is to analyze the link of fractalkine levels in NeuroBechet's disease and multiple sclerosis (MS) for examine whether this chemokine has a possible diagnostic or a teuropathic target. Twenty NBD, 25 relapsing- remitting MS, 15 chronic progressive MS, 15 clinically isolated syndrome, 14 radiological isolated MS patients and 30 healthy controls have been included in this study. Serum samples has been measured using enzyme-linked immunosorbent assay (ELISA) method.

As a result, serum levels of CX3CL1 were significantly high in RRMS than other groups. Compared with healthy control groups there wasn't any significant difference between NBD group but again in MS groups fractalkine levels were shown high levels. These results suggest that, NBD is a nonspecific inflammatory condition compared to autoimmune mediated disorders such as MS. In literature fractalkine was studied especially in Alzheimer's

disease and it was shown that CX3CL1 has various effects. It can suppress the production of nitric oxide (NO). NO, related to the increased levels of IFN- $\gamma$  and TNF- $\alpha$ . Also it released from hippocampal cells after excitotoxic insult has an essential role in brain protection by reducing against glutamate mediated excitotoxicity. Moreover CX3CL1/CX3CR1 regulate the activation of microglia by controlling the release of inflammatory cytokines and synaptic plasticity and cognitive functions by modulating receptors in neurons. Consequently in inflammatory conditions this chemokine has a noteworthy role for neuroprotection and antiinflammation. We also shown that CX3CL1 has a possible target for monitoring the prognosis of MS patients and in future it will be a promising new therapeutic target.

### Disclosure

Ceyla Irkec et al.: Nothing to disclose

### EP1491

#### 25 hydroxyvitamin D and cytokines in Bulgarian patients with multiple sclerosis

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**Background:** Experimental and clinical studies have demonstrated immunomodulatory effect of vitamin D on the risk of developing experimental allergic encephalomyelitis (EAE), multiple sclerosis (MS) and correlation with the neurological deficit. Disputable questions are: vitamin D serum concentration necessary to suppress the immune response; subgroup of MS patients suitable for vitamin D treatment; optimal effective balance between and safe dosage of vitamin D.

**Objective:** To evaluate changes in serum concentration of 25(OH)D, IL4, IL10, TGF $\beta$ 1, IL17A, IFN- $\gamma$ , TNF- $\alpha$  in MS relapse and remission, and their correlation with patients' degree of disability.

**Methods:** A prospective, case-control study comprised 86 persons (18-50 years age) from Caucasians community dwelling at 41.5-42 northern latitude, who were registered during the astronomical winter period (October-May). Within these: 46 patients with relapsing-remitting MS (RRMS) according to McDonald criteria (2010), mean age 37 $\pm$ 1.83 years, mean disease duration 7.17 $\pm$ 1.17 years, Expanded Disability Status Scale (EDSS) score 1.5-5.0; 40 healthy controls matching by age and gender. Serum 25(OH)D and cytokine concentrations were measured by ELISA. Statistical methods: alternative, variance analysis, nonparametric test, correlation analysis and multiple linear regression analysis.

**Results:** RRMS patients had considerably lower serum levels of 25(OH)D than the healthy controls ( $p=0.09$ ); 25(OH)D concentrations within the deficiency range for Bulgarian population ( $\leq 25$  nmol/l) were detected in 71.7% of the patients during relapse; serum 25(OH)D was significantly higher in clinical remission than in relapse phase ( $p=0.024$ ). A significant negative correlation was found between 25(OH)D levels and EDSS in relapse ( $r=-0.416$ ,  $p=0.004$ ); 25(OH)D deficiency increased the risk of MS 3.43 times.

Significantly higher IL4, TGF $\beta$ 1 and lower IFN- $\gamma$  levels were found in remission compared to relapse ( $p=0.006$ ,  $p=0.009$ ,  $p=0.017$ ).

Multiple Linear Regression Analysis established 25(OH)D, TNF $\alpha$ , IL17A as significant, independent factors determining EDSS score in relapse.

**Conclusion:** Our study showed a protective effect of 25(OH)D on the neurological deficit and the risk of developing the disease in Bulgarian patients with RRMS. Thus further studies are necessary to elucidate the therapeutic potential of 25(OH)D to modify the disease course.

### Disclosure

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Ivanka I. Kostadinova-nothing to disclose

Zahari I. Zahariev-nothing to disclose

### EP1492

#### Vascular inflammation markers in multiple sclerosis: possible role in oligoclonal band formation

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Vascular inflammation has been shown to be involved in conditions that promote chronic systemic inflammation, such as obesity, cancer, autoimmune and infectious diseases. Vascular inflammation is regulated by endothelial adhesion molecules, chemokines and inflammasome components that are expressed mostly by endothelial cells and pericytes. In this study, we aimed to analyze the significance of serum and cerebrospinal fluid (CSF) levels of vascular inflammation parameters in pathogenesis and development of multiple sclerosis (MS).

A total of 19 relapsing remitting MS (RRMS) patients, 18 clinically isolated syndrome (CIS) patients and 20 healthy controls were recruited for this study. Patients were in remission and were not under immunosuppressive treatment during serum and CSF sampling. Disease durations, EDSS scores, relapse numbers and oligoclonal band (OCB) status of all patients were recorded. Serum and CSF levels of tissue inhibitor of metalloproteinases-3 (TIMP3), matrix metalloproteinase 9 (MMP9), a disintegrin and metalloproteinase domain-containing protein 15 (ADAM15), platelet derived growth factor-BB (PDGF-BB), NOD-like receptor protein 1 (NLRP1) and NLRP3 were measured by ELISA.

There were no significant differences between serum and CSF levels of CIS and RRMS patients by means of vascular inflammation parameters, while both groups had higher levels of all parameters as compared to healthy controls. CSF but not serum PDGF-BB, MMP9, NLRP1 and NLRP3 levels of OCB positive RRMS patients were significantly higher than those of OCB negative patients. There was no correlation between serum/CSF vascular inflammation parameters and clinical-demographic features of RRMS patients.

Vascular inflammation appears to be activated as early as during the first MS attack. However, levels of vascular inflammation parameters are not altered in a time- or disability-dependent manner and thus cannot be used as indicators of MS conversion or as a prognostic biomarker. Increased CSF levels of OCB positive patients might be due to enhanced blood-brain barrier

permeability and subsequently increased transport of myeloid cells or glial cell activation.

### Disclosure

Recai Türkoğlu: nothing to disclose  
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Erdem Tüzün: nothing to disclose.

### EP1493

#### Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies in Turkish population: a comparative study

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**Background:** Most patients with NMO/ NMOSD have autoantibodies against aquaporin-4 (AQP4-Ab), but recently, myelin-oligodendrocyte glycoprotein antibodies (MOG-Abs) have been found in some patients with childhood and adult demyelinating diseases.

**Aim:** To evaluate the clinical features of patients with NMO/ NMOSD with MOG-Ab and to compare them with patients with AQP4-Ab-positive NMO/ NMOSD, and multiple sclerosis.

**Methods:** This observational study was conducted at Dokuz Eylül University Hospital in specialist center for demyelinating disease. We examined AQP4 antibody and MOG antibody in 62 NMO/ NMOSD and 33 Multiple sclerosis (MS) patients with ON. Groups were statistically matched age, gender, onset age, disease duration and disease severity. The diagnosis of NMO/ NMOSD was made according to Wingerchuck criteria (2006). Cell-based assays were used to test patient serum samples for AQP4-Abs and MOG-Abs.

**Results:** None of thirty-three MS patients with ON had AQP4-Ab and MOG antibody. Five patients with atypical aggressive demyelinating disease had both antibodies. In one of 3 ADEM patients with LETM, MOG-Ab was positive (all AQP4-Ab negative). In only one of 17 LETM patients, MOG-Ab was positive and all of them was NMO-IgG negative. MOG antibody was not detected in any of 23 NMO patients with AQP4-Ab. In 2 of 10 relapsing ON patients MOG antibody and in 1 of the remaining patients AQP4-Ab was positive. These patients presented with simultaneous/sequential severe ON. Only one of 4 patients with area postrema syndrome had AQP4-Ab and none of them had MOG-Ab. Cerebrospinal fluid characteristics were different in the MS and NMO/ NMOSD groups. OCBs were determined in 83% of MS patients and none of NMO/ NMOSD had OCBs.

**Conclusion:** Only 4.8% of all patients in NMOSD group and 6.6% of patients in AQP4-Ab negative group had MOG-Ab. A higher proportion of AQP4-Ab-positive patients relapsed than MOG-Ab positive group despite similar follow-up durations but onset episode severity and outcomes from the onset episode did not differ between the 2 groups. MS had neither AQP4- Ab nor MOG-Ab.

### Disclosure

Egemen İdman had no conflict of interest.  
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Hatice Limoncu had no conflict of interest.  
Onur Bulut had no conflict of interest.  
Zekiye Altun had no conflict of interest.

### EP1494

#### Carotid intima-media thickness is associated with HLA-DRB1\*15 in multiple sclerosis

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**Background:** There is a growing evidence that endothelial function could be involved in the pathogenesis of multiple sclerosis (MS). Previous reports have shown its role in other autoimmune disorders like rheumatoid arthritis.

HLA-DRB1\*15 induces a double risk for having MS. Furthermore, in relapsing-remitting MS (RRMS) several markers of inflammation have been associated with the severity of disease. We have investigated the endothelial damage in MS patients measuring carotid intima-media thickness (cIMT) and its correlation with the levels of inflammation biomarkers.

**Methods:** A total of 37 patients with RRMS, aged  $40.90 \pm 8.6$ , median EDSS= 2.0 (range 3.5), were recruited according to McDonald's 2010 criteria for MS diagnosis. After informed consent, cIMT was measured in these patients, with no other classical vascular risk factors. Ultrasonographic images were obtained by a blind examiner with an Accuson X300 PE (Siemens) device according with ultrasounds protocol. IMT was determined as the average of at least three different measurements in the common carotid artery. DNA was obtained from peripheral blood by using a semi automated method. HLA antigens typification was performed by polymerase chain reaction with sequence-specific oligonucleotides (PCR-SSO) and Luminex analysis. Several biomarkers of inflammation were also analysed with the Milliplex system in a Luminex 200 platform. For the statistical analysis, SPSS v15 was used. Categorical variables were analyzed using Chi2 method, and Student T test were used for continuous variables. ROC curve was calculated to determine the sensibility and specificity of the cIMT in predicting those HLA-DRB1\*15 positive MS patients.

**Results:** EDSS score and demographic features (sex) versus presence of HLA-DRB1\*15. Patients with the HLA-DRB1\*15 allele (n=14) had cIMT 0.116 mm thicker (mean  $1.044 \pm 0.15$ ) than those lacking this allele (mean  $0.928 \pm 0.15$  mm;  $p=0.0041$ ). There was no correlation between the HLA-DRB1\*15 allele and several biomarkers of inflammation (Reactive C Protein, Erythrocyte Sedimentation Rate, fibrinogen or von Willebrand Factor).

**Conclusion:** For the first time, we found an association of HLA-DRB1\*15 with endothelial damage (cIMT) in patients having RRMS. We hypothesized that endothelial dysfunction could be



correlated with inflammation and disease activity. Further and larger studies should be performed to confirm this association.

### Disclosure

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M Toriello-Suárez: Nothing to declare.

J. Gonzalo Ocejo-Vinyals: Nothing to declare

S Gutierrez González: has received support for travel to medical meetings from Almirall.

J Irure Ventura: Nothing to declare.

S Pérez-Pereda: Nothing to declare

F Ausín-Ortega: Nothing to declare

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### EP1495

#### Gut microbiota alteration in Clinically Isolated Syndrome: a pilot study

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**Background:** Relatively little is known about what might trigger or facilitate the first episode of demyelization in Multiple Sclerosis (MS); recent data indicate that the dysregulation of the immune system that occurs in MS could be controlled by environmental factors. The composition of the gut microbiota structure in terms of species richness and distribution, as well as the functional potential of the community, can greatly impact the host immune system; an imbalance in the gut microbiome has been shown to induce a profound alteration of immune responses both in the gut-associated tissue and in the periphery and could be a risk factor for MS.

**Aims:** As the Clinically Isolated Syndrome (CIS) allows to study the disease processes closest to the biological onset of MS, the aim of this pilot project was to investigate whether alteration in the composition of the gut microbiota could be associated with CIS and its immune system alteration.

**Methods:** Stool and blood samples were collected from 20 CIS patients and 20 Healthy Volunteers (HV). DNA isolated from stools were subjected to shotgun metagenomic sequencing strategy in order to discover the microbiota composition as well as the microbial function. T helper (Th)17 and T regulatory (Treg) cells were analyzed by FACS in the peripheral blood (PB).

**Results:** Our preliminary results indicate a lower abundance of *Bacteroides* and a decrease species richness in CIS patients versus HV. In the PB, CIS patients displayed an increase of pathogenic Th17 cells expressing Toll Like Receptor 2 and a decrease of Treg cells producing Interleukin-10 and expressing CD39 compared to HV.

**Conclusions:** These findings indicate that gut microbial dysbiosis could exist at the onset of MS and could be suggestive of a pro-inflammatory milieu observed in the periphery. The analysis on metagenomic content and microbial gene identification will allow us to determine the presence/abundance of specific genes that

can be correlated with CIS in order to design strategies to modulate the immune system through alteration of gut microbiome.

### Disclosure

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### EP1496

#### Does vitamin D facilitate a chronic inflammatory response in multiple sclerosis

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**Background:** Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nerve system. Multiple types of immune cells have been associated with MS aetiology, including monocytes, B cell and T helper (Th) cell subsets. The potential interaction between peripheral immune cells, Vitamin D and MS could affect the pathogenic mechanisms of MS and is the focus of this study.

**Objectives:** To investigate the association between peripheral immune cell responses, Vitamin D and MS *ex vivo* and *in vitro* in a case-control study.

**Methods:** We collected peripheral blood mononuclear cells (PBMCs) from 62 people with MS and 12 healthy controls (HC), and determined the proportion of immune cell subsets via Flow cytometry *ex vivo*. Furthermore, we stimulated isolated PBMCs with ConA (10µg/ml), ConA + 25(OH)D3 (500nM) or ConA + 1,25(OH)2D3 (100nM) for 96h *in vitro*. The Th cell subsets were analysed via Flow cytometry and the titer of cytokines in supernatants was determined via Cytometric Bead Array. The genotypes of Vitamin D-associated MS risk-SNPs (rs12368653, rs703842, rs2248359) were determined by 3' mismatch PCR. Data were compared using nonparametric tests (i.e., Mann-Whitney, Kruskal-Wallis and Friedman test).

**Results:** *Ex vivo*, the proportion of classic monocytes was decreased in monocytes ( $p=0.0144$ ), while the proportion of B cell was increased in PBMCs ( $p=0.0089$ ) in the MS cohort than in HC. In *in vitro*, for the whole samples, both 25(OH)D3 and 1,25(OH)2D3 significantly inhibited the production of IL-6 ( $p<$

0.01), IL-10 ( $p < 0.001$ ), TNF ( $p < 0.001$ ), IFN- $\gamma$  ( $p < 0.001$ ) and IL-17A ( $p < 0.001$ ), and promoted the production of IL-4 ( $p < 0.01$ ) by PBMCs after 96hrs of stimulation with ConA. Interestingly the HI PBMCs produced more IL-6 ( $p = 0.0171$ ), TNF ( $p = 0.0001$ ) and Th1 ( $p = 0.0231$ ) after stimulation with ConA for 96h than the MS group. The rs703842 risk allele AA was associated with significantly reduced production of IL-2 at 96h ( $p = 0.0076$ ). For the whole samples, the rs2248359 risk allele TT was associated with an increased proportion of Th17 and Th1 cell populations within the CD4+ T cell subset *ex vivo* and the Th1 population after 96h ConA stimulation (*in vitro*).

**Conclusions:** Peripheral immune cell variations and inflammatory cytokine profiles are influenced by Vitamin D and the MS status *ex vivo* and *in vitro* supporting a potential role for vitamin D in the pathogenesis of MS.

**Keywords:** peripheral immune cell subsets, Vitamin D, cytokines.

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Ming Lu: nothing to disclose

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### EP1497

#### Osteopontin plasma levels in relapsing remitting multiple sclerosis

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**Background:** Multiple sclerosis (MS) is known as a neuro-inflammatory disease of the central nervous system (CNS). The neuroinflammation may induce pro-inflammatory cytokines such as the Osteopontin (OPN). OPN plays an important role in the inflammation by regulating the THelper1 and THelper17 responses. Since diagnosis of multiple sclerosis is somewhat of a challenge, a reliable diagnostic biomarker that can be easily measured would be a great diagnostic method.

**Objective:** In this study we compared OPN plasma levels in adult relapsing remitting multiple sclerosis (RRMS) patients.

**Method:** In a case-control study, plasma was collected from the relapsing-remitting multiple sclerosis patients (RRMS) ( $n = 36$ ) as well as 35 age matched healthy individuals and a control group. Levels of OPN were measured and compared between the two groups.

**Result:** Mean OPN plasma levels was markedly higher in the case group (Mean [SEM], 4240[201.5] pg/ml) compared with the control group (3419[264.5]) ( $p$ -value=0.008).

**Conclusion:** Significant higher OPN plasma levels in Relapsing-remitting multiple sclerosis patients suggest that OPN can be used as a diagnostic biomarker.

**Keywords:** Multiple Sclerosis, Relapsing-remitting multiple sclerosis, Osteopontin, Plasma

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### EP1498

#### Immunity in NeuroBehcet disease

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**Introduction:** NeuroBehcet disease (NBD) is the most frequent vasculitis in our country. In presence of inaugural neurological forms, CSF study is systematic because of diagnosis difficulties.

**Objectives:** To describe the immunoelectrophoretic and cytokine profile in NBD

**Patients:** Criteria of selection: NBD according to the International consensus recommendation (ICR) with definite and probable forms including isolated neurological syndrome suggestive of NBD. Subjects were consecutive patients who referred to Neurological department of Charles Nicolle hospital since 2013. Blood and CSF samples are taken from all patients. Cell counting, protein analysis, immunoelectrophoretic profile with Ig G Index was performed. Cytokines levels were evaluated by PCR.

**Result:** From 26 NBD recruited 17 had an inaugural neurological form of which 15/17 had a parenchymal involvement. The IgG index was increased in only 2 patients (8%). At the Immunoelectrophoresis, the profile was type 1 in 22 patients (81%), type 2 in 1 patient (3.7%) and type 3 and 4 in 4 patients (11%). The study of lymphocyte populations showed an increase of IL-17, interferon gamma and IL10 levels in 88% of patients.

**Discussion:** The profile data in CSF of NBD patients in our study are in line with those found in the literature. Given the limited data on CSF levels of cytokines in patients with NBD, our results showed that cytokines make a pivotal role in pathogenesis of NB, as evidenced by the conjoining increase of pro and anti-inflammatory cytokines in our patients.

**Conclusion:** Activation of self-reactive T cells with involvement of cytokines and proinflammatory transcription factors is currently proven in NBD. Implication of B cells can be also proved by the presence of oligo-clonal bands.

### Disclosure

Nothing to disclose

## Microbiology and Virology

### EP1499

#### HLA-DRB1\*15:01 confers susceptibility to Epstein-Barr virus infection to B cells linking genetic and environmental risk factors for multiple sclerosis

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**Background:** Whereas the exact pathogenesis of multiple sclerosis (MS) is still not understood, it is generally accepted that MS results from an interplay of genetic and environmental factors. The strongest genetic risk factor for MS is the human leukocyte antigen (HLA) class II allele HLA-DRB1\*15:01. The strongest environmental risk factor for MS is infection with the B

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lymphocytotropic herpesvirus Epstein-Barr Virus (EBV). Although it is well-known that EBV uses HLA-DQ, -DR and -DP as co-receptors for infection of B cells, it was hitherto unknown whether HLA-DRB1\*15:01 may act as a co-receptor for EBV infection.

**Objective:** To investigate whether HLA-DRB1\*15:01 confers susceptibility to EBV infection to a B cell line *in vitro*.

**Methods:** We transfected the HLA-DR deficient B lymphoblastoid cell line 721.174 (LCL721.174) with plasmids expressing HLA-DRB1\*15:01, HLA-DRB1\*13:03, HLA-DRB1\*11:01 and DRB1\*01:01 and subsequently infected these cells with a recombinant EBV encoding green fluorescent protein (EBV-GFP). The percentage of EBV-infected cells (i.e. GFP-positive cells) among HLA-DR expressing cells was determined by flow cytometry.

**Results:** While untransfected LCL721.174 and LCL721.174 transfected with an empty vector were not infectable with EBV-GFP, transfection with HLA-DRB1\*15:01 conferred susceptibility to EBV infection to LCL721.174. There was a trend for a higher percentage of EBV-infected LCL721.174 among HLA-DRB1\*15:01 compared to HLA-DRB1\*13:03, HLA-DRB1\*11:01 and DRB1\*01:01 expressing LCL721.174 ( $p=0.2$ , Kruskal-Wallis test).

**Conclusion:** Our findings show that EBV uses HLA-DRB1\*15:01 as a co-receptor for infection of B cells *in vitro*, pointing towards a potential mechanistic link between the strongest genetic and environmental risk factors for MS. Future studies should clarify how different HLA class II alleles influence the susceptibility of B cells to EBV infection *in vivo*.

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## EP1500

### Herpes virus and varicella zoster virus antibodies Index in the cerebrospinal fluid of patients with multiple sclerosis patients and clinically isolated syndrome

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Varicella Zoster Virus (VZV) and Herpes Virus (HSV) are proposed to play a role in the pathogenesis of Multiple Sclerosis. The presence of virus-specific antibodies in the CSF suggests that demyelination in MS is accompanied by antiviral immune responses mounting an altered immune response against viruses, in CNS. The purpose of the study was to evaluate the presence of VZV and HSV antibodies in patients with Multiple Sclerosis (MS) and Clinically Isolated Syndrome (CIS) both in serum and cerebrospinal fluid.

**Methods:** Ninety four patients with Multiple Sclerosis were studied. Fifty seven patients had relapsing remitting MS (RRMS),

37 patients had clinically isolated syndrome (CIS) and two with radiologically Isolated Syndrome. The presence of VZV and HSV antibodies was tested in the serum and cerebrospinal fluid (CSF) of all patients

**Results:** HSV IgG and VZV IgG were detected at increased levels in serum in patients with RRMS (HSV IgG  $132.8 \pm 44.8$ , VZV IgG  $488.4 \pm 165.8$ ) and CIS (HSV IgG  $105.2 \pm 54.67$ , VZV IgG  $489 \pm 165.7$ ). However, the VZV IgM and HSV IgM levels in serum were low.

In CSF, IgG values  $>1.5$  were considered to be indicative of intrathecal IgG production against the respective pathogen. IgG index of HSV and VZV in RRMS was marginally positive in low levels ( $1.4 \pm 0.9$  and  $0.8 \pm 0.9$  respectively). IgG index of HSV and VZV in patients with CIS was  $1.1 \pm 0.9$  and  $0.6 \pm 0.4$  respectively. No patient had indication of viral infection in CSF. No HSV IgG was detected in CSF of RIS patients

However, increased HSV IgG index in CSF ( $>2$ ) was found in 12/57 patients with RRMS. PCR for VZV and HSV in CSF was negative. 5/12 (41%) had negative oligoclonal bands while from RRMS patients with negative HSV and VZV index in CSF only 4/45 (9%) had negative oligoclonal bands,  $p=0.01$ . Five patients with CIS had increased HSV IgG index. 3/5 CIS patients and 7/12 RRMS patients with positive HSV IgG index in CSF were in relapse with gadolinium enhancement in MRI.

**Conclusion:** The positivity of HSV and VZV IgM antibodies in CSF of MS patients without any sign of infection, might support a role of immune response against viruses in disease pathogenesis.

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## Environmental factors

### EP1501

#### Dietary intakes of minerals and disability in multiple sclerosis; is there any association?

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**Introduction:** Multiple sclerosis (MS) is a chronic demyelinating disease of the nervous system which is the most common cause of neurological irreversible disability in young adults who are professionally and socially active persons. It expresses itself in three clinical forms: relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). Assessment of dietary intakes of mineral is an approach that has been used to evaluate diet-disease and diet-disability association.



**Method:** 126 patients with diagnosed MS (84 RRMS, 21 PPMS and 21 SPMS) with MRI assessment of brain and spinal cord were recruited from multiple sclerosis clinic in Kashani Hospital of Isfahan University of Medical Sciences, Isfahan, Iran include from present cross-sectional study. A 168-item semi-quantitative food frequency questionnaire was used for assessment of dietary intakes of minerals. Medical history questionnaire, Expanded Disability Status Scale (EDSS) and Fatigue questionnaire record from all participants.

**Results:** Mean  $\pm$  SD of EDSS and fatigue scale in SPMS and PPMS groups was significant higher than RRMS group. In addition, there was a negative significant association between magnesium and phosphorous with fatigue scale among all participants; ( $r=-0.684$ ;  $p<0.001$ ) for magnesium and ( $r=-0.792$ ;  $p<0.001$ ) for phosphorous, as well as calcium and fatigue scale in RRMS ( $r=-0.921$ ;  $p<0.001$ ). In addition there was a negative significant association between selenium with EDSS in RRMS ( $r=-0.490$ ;  $p<0.001$ ) and PPMS ( $r=-0.896$ ;  $p<0.001$ ). Age, gender and blood pressure were not confounder variables. In addition, we adjusted energy intakes in subgroups.

**Conclusion:** Our study demonstrated that there is a negative significant correlation between intakes of magnesium and phosphorous with fatigue scale among all participants that may due to the role of this mineral in energy metabolism. In addition dietary intakes of selenium can decrease EDSS in RRMS and PPMS. Further studies with larger sample sizes and other population needed to prove this correlation.

**Keywords:** multiple sclerosis, mineral, disability

## Disclosure

The authors declared no conflict of interest.

## EP1502

### Clinical relevance of Vitamin D and cholesterol serum levels in multiple sclerosis: a real-word data study

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**Objective:** Vitamin D (VitD) is known to influence immune system function and multiple sclerosis (MS) susceptibility. Modulation of serum cholesterol (Chol) level has been shown to impact on brain atrophy in MS. This study wanted to investigate correlation between VitD and Chol in MS and their association with MS activity and disability progression (DP).

**Methods:** We reviewed medical records, laboratory data and MRI of subjects newly diagnosed with MS at our specialist center between January 2014 and February 2017.

We analyzed association between hypovitaminosis D (HypoD) and hypercholesterolemia (HyprCh) with MRI activity (MRIa) when blood sampling and imaging acquisition were less than 120 days (d) apart, and between HypoD or HyprCh less than 120d apart from 1<sup>st</sup> clinic assessment with occurrence of relapses, MRIa and DP at follow up (mean 492d, range 0-2260d).

Finally, we evaluated correlation between VitD and Chol measured in the same sample at all time-points.

We defined HypoD as VitD  $<30$  nmol/L, HyprCh as Chol  $>5$  mmol/L, DP as increase of EDSS  $\geq 1$  point after up to 2 years and MRIa as presence of T1 gad-enhancement and/or new T2 lesions.

**Results:** 72 patients were included (71% female, mean age  $44 \pm 14$  years); 30% were receiving disease modifying treatment, 15% statins and 70% VitD supplements (VitDs).

Baseline MRI was performed  $\approx 120$  d before 1<sup>st</sup> clinic attendance (Median -123d, -2937d-239d); 2<sup>nd</sup> MRI was performed a median of 364d (41d-2652d) after 1<sup>st</sup> MRI; 3<sup>rd</sup> MRI was done a median of 392d (50d-1344d) after 2<sup>nd</sup> MRI.

Baseline HypoD significantly associate with occurrence of relapses during follow up ( $\chi^2, p<0.05$ ). HypoD does not associate significantly with MRIa at any time-point nor with DP at 2 years; a trend was observed for association between HypoD and new T2 lesions in 2<sup>nd</sup> MRI ( $\chi^2, p=0.08$ ). MS patients who had 3<sup>rd</sup> MRI had normal VitD (69% on VitDs).

HyprCh at baseline and follow up did not associate with MRIa, occurrence of relapses or DP at any time point; a trend was observed for association of HyprCh and new T2 lesions in 3<sup>rd</sup> MRI ( $\chi^2, p=0.06$ ).

Serum VitD inversely correlate with Chol (Pearson's  $r=0.22$ ,  $p<0.01$ ).

**Conclusion:** HypoD impacts on early MS clinical activity and VitD and Chol serum levels are inversely correlated. This evidence support the need for further studies looking at the effect of VitD and Chol on MS pathophysiology and clinical course.

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## EP1503

### Fats and multiple sclerosis; association between fats/oils intake and disability in patients with MS

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**Introduction:** Multiple sclerosis (MS) is a chronic demyelinating disease of the nervous system which is the most common cause of neurological irreversible disability in young adults who are professionally and socially active persons. Due to the variable clinical course of MS, it is classified into relapsing and progressive phases and three phenotypes of relapsing remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). Assessment of dietary intakes of fats is an approach that has been used to evaluate diet-disease and diet-disability association.

**Method:** 126 patients with diagnosed MS (84 RRMS, 21 PPMS and 21 SPMS) with MRI assessment of brain and spinal cord were recruited from multiple sclerosis clinic in Kashani Hospital of Isfahan University of Medical Sciences, Isfahan, Iran include from present cross-sectional study. A 168-item semi-quantitative food frequency questionnaire was used for assessment of dietary intakes of fatty acids. Medical history questionnaire, Expanded Disability Status Scale (EDSS) and Fatigue questionnaire record from all participants.

**Results:** Mean  $\pm$  SD of EDSS and fatigue scale in SPMS and PPMS groups was significant higher than RRMS group. There was a negative significant correlation between intakes of Poly Unsaturated Fatty Acids (PUFAs) including Linolenic Acid ( $r=-0.418$ ,  $p=0.018$ ), Linoleic Acid ( $r=-0.312$ ,  $p=0.031$ ) with EDSS in all participants. In addition, There was a negative significant correlation between intakes of Mono Unsaturated Fatty Acids (MUFAs) ( $r=-0.348$ ,  $p=0.028$ ) with EDSS in all participants. Correlation between Saturated Fatty Acids (SFAs) with EDSS ( $r=0.465$ ,  $p=0.009$ ) and fatigue scale ( $r=0.298$ ,  $p=0.043$ ) was significantly positive in all participants. Although correlation between total dietary fats with EDSS and fatigue scale in all participants and subgroups were positive, but was not significant. Age, gender and blood pressure were not confounder variables. In addition, we adjusted energy intakes in subgroups.

**Conclusion:** Our study demonstrated that there is a positive significant correlation between intakes of SFAs with EDSS and fatigue scale in all participants. In addition dietary intakes PUFAs and MUFAs can decrease EDSS in all patients with MS. Further studies with larger sample sizes and other population needed to prove this correlation.

**Keywords:** Expanded Disability Status Scale, Fatigue, Poly Unsaturated Fatty Acids, Mono Unsaturated Fatty Acids, Saturated Fatty Acids

#### Disclosure

The authors declared no conflict of interest.

#### EP1504

##### Vitamin D level and quality of life in patients with multiple sclerosis

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**Object:** Vitamin D status is associated with the incidence and prevalence of a variety of neurologic disorders, including multiple sclerosis. Several studies suggest or support that multiple sclerosis has increased prevalence in geographic areas with lower sunlight levels. We aimed to investigate the correlation between vitamin D level and quality of life in patients with multiple sclerosis who were exposed to sunny seasons within one year in western Turkey.

**Method:** This follow-up study included 200 MS patients with a serum baseline 25(OH)D3 level, Expanded Disability Status Scale (EDSS) and multiple sclerosis quality of life questionnaire (MSQOL-54) with a follow-up of one year. Serum 25(OH)D was classified into the following categories: less than 25, 25-50, and 50 nmol/L or greater. Patients with vitamin D levels less than or equal 30ng/ml were administered vitamin D supplementation with an average weekly dose of 50.000 IU until vitamin D levels became normal, and then maintenance daily dose of 4000 IU. All patients underwent interview and MSQOL-54 was evaluated at baseline, 1 month, 3 months, 6 months, and 12 months after the beginning of vitamin D administration.

**Results:** Of 200 multiple sclerosis patients, 185 (92.5%) had lower vitamin D level. Patients reported no side effects during the study. The increase in Vitamin D level from baseline to 12 months was significant ( $p < 0.0001$ ). The improvements remained significant in all categories of MSQOL-54 after the vitamin D

administration ( $p < 0.001$ ). According to our results, the longer vitamin D use the higher improvement of quality of life.

**Conclusion:** Little is known regarding the effect of vitamin D supplementation on quality of life. Also, the evidence for a beneficial effect of long-term vitamin D supplementation on health-related quality of life is lacking. This study showed that the prevalence of vitamin D level is still low in geographic areas with higher sunlight levels, and also, when vitamin D deficiency or insufficiency was corrected, there was indeed a positive effect on quality of life of patients.

#### Disclosure

nothing to disclose

## Neurobiology

#### EP1505

##### Moving from systemic to central nervous system inflammation: the role of A20 in the neuropathology of multiple sclerosis

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Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) in which inflammation plays a key pathological role. The anti-inflammatory enzyme A20 is considered a central gatekeeper in inflammation and immunity through the inhibition of NF- $\kappa$ B. Polymorphisms in A20 genomic-region has been recently associated to MS and we observed an A20 down-regulation in peripheral blood cells of MS patients, mainly due to monocytes, correlated to a worst clinical course.

Recent evidences showed that systemic inflammation induces increasing cell infiltration within the brain parenchyma, triggering resident microglial and astrocytic activation. Considering the critical role of A20 in systemic inflammation regulation, a function of A20 in the CNS was hypothesized. Supporting this, the presence of A20 transcript and proteins belonging to A20-complex were newly demonstrated in control human brain. Moreover, A20 deletion in neuroectodermal cells worsen the clinical course of the MS murine model. From this picture, clearly emerges a double role of A20 in central nervous and immune system.

Here we aimed to unveil the contribution of A20 to the CNS MS pathology, studying for the first time A20 expression in human *post-mortem* MS brain tissues.

We demonstrated that A20 is present in control human brain tissues in both white matter, mainly in parenchymal astrocytes and in grey matter, in neuronal cells. In MS brain, we observe a massive A20 expression in the lesions in both perivascular infiltrates and ramified cells. In particular, in active and pre-active lesions, A20 is

expressed in the active core, whereas in chronic active lesions, A20 is mainly expressed on the active-margin. Preliminary double immunofluorescence staining unveiled that A20 is expressed in both AL and CAL by infiltrating macrophages and by resident activated astrocytes and a subpopulation of microglial cells. Coherently, chronic activation of NF- $\kappa$ B pathway in infiltrating and resident CNS seems an hallmark of the neurodegenerative process occurring in MS patients. In this view, the massive A20 activation in the active plaques could represent a defensive mechanism contributing to the inflammation resolution and the regeneration processes.

### Disclosure

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Panzica: has nothing to disclose

Bertolotto: has nothing to disclose

### EP1506

#### The unglycosylated KIR4.1 extracellular domain constitutes an autoimmune target in multiple sclerosis and can promote demyelinating encephalomyelitis in mice

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**Background:** Multiple sclerosis (MS) involves immune cells including B and T cells but the actual targets of the immune response are still undefined. The ATP-sensitive inward rectifying potassium channel KIR4.1 expressed by glial cells is suspected as an autoantigen since high seric levels of IgG against its extracellular peptide sequence (e1) were reported in half of MS patients. Yet, high discrepancies in frequencies (0-28 %) exist among laboratories raising concerns about KIR4.1 as a valid marker and autoantigen candidate for MS. They may result from technical pitfalls or different protein conformations differentially recognised by the antibody.

**Methods and results:** Using ELISA with the synthetic e1 sequence as coating peptide, we obtained very high seric levels of anti-e1 IgG from e1-immunised mice with no signal from control mice. Concomitantly, we screened human sera for the presence of anti-e1 hIgG from 71 patients diagnosed for a Clinically Isolated Syndrome (CIS), 193 untreated MS patients and 130 Healthy Volunteers (HV). We found that 5.3 % of CIS/MS patients exhibit high levels of KIR4.1 antibodies (defined as high responders - HR - using a threshold of 2.5 SD above HV mean) vs. 0.7% in HVs ( $p < 0.02$ ). Moreover, the anti-e1 mouse serum labeled scarce astroglial cells and slightly white matter glial fibers in the normal rodent and human brain, with increased labeling in MS brain. Specific immunolabeling using anti-e1 mouse serum or a HR serum was obtained on cultured human astrocytoma, particularly when glycosylation

was inhibited *in vitro*. Western Blot of astrocytoma extracts showed that the anti-e1 serum recognised the unglycosylated form of KIR4.1 but not higher molecular weight forms. Immunisation with e1 peptide results in the late development of experimental autoimmune encephalomyelitis in 1/3 of the mice.

**Conclusions:** These data demonstrate in a subset of MS patients the presence of anti-Kir4.1 auto-antibodies directed against the unglycosylated protein, which is increased in MS lesions. The development of demyelinating neuroinflammation in e1-immunised mice supports KIR4.1 as an autoantigen. Our results favor the heterogeneity in the autoimmune aspect of the disease, in which subgroups with discrete IgG autoreactivities for CNS antigens may be further delineated in the MS spectrum.

### Disclosure

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### EP1507

#### Tart cherry extract as a powerful substance to ameliorate oxidative stress in the cuprizone model

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Myelin sheaths of central nervous system (CNS) are multilayered and are enriched in lipids and proteins. Any perturbation in myelin protein expression or structure might contribute to disassembly of the myelin sheath. It is speculated that specific chemicals found in cherries could reduce pain, modulate inflammation, and exert antioxidative effects. The aim of the current study was to evaluate the effect of pure p-coumaric acid as a potent antioxidant agent, and tart cherry extract ingestion on the expression of the oxidative stress sensor Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and the myelin homeostasis factor myelin basic protein (MBP) during cuprizone-induced de- and remyelination.

Acute demyelination was induced by feeding young mice for 6 weeks with cuprizone mixed into ground rodent chow. At week 6, animals were returned to normal chow for up to 6 weeks to allow endogenous remyelination. Animals were sacrificed after acute demyelination as well as after 3 and 6 weeks of recovery. Mice were categorized into three groups: normal chow, tart cherry or p-coumaric acid. HPLC was used to quantify p-coumaric acid levels in entire tart cherry extracts. To estimate levels of oxidative stress and myelin recovery, we quantified Nrf2 and MBP gene expression levels by means of rt-PCR in the isolated brains. Results were compared to control animals not intoxicated with cuprizone.



In male mice, Nrf2 expression was induced at week 6 and 9, and thereafter was found to be downregulated. Recovery of Nrf2 expression was accelerated in tart cherry treated groups. p-coumaric acid had an intermediate effect on Nrf2 expression. Amelioration of Nrf2 expression in tart cherry treated groups was paralleled by a pronounced induction of MBP expression. This was not observed in p-coumaric acid treated groups. Interestingly, these effects were specific for male mice, and were not observed in female mice.

In summary, this study clearly illustrates a potent anti-oxidative effect of tart cherry extracts in a model for de- and remyelination. Beyond, remyelination might be accelerated by tart cherry extract treatment. Future studies now have to show which pathways and cell types are involved in this protective effect.

#### Disclosure:

This research was done by personal funding

## Neurodegeneration

### EP1508

#### The effect of simvastatin on autophagy in mammalian cells

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**Background:** Multiple sclerosis (MS) is a chronic autoimmune condition of the central nervous system associated with demyelination and neurological impairment. Autophagy is a mechanism of intracellular lysosomal degradation of dysfunctional cytoplasmic components. It plays a critical role in the functioning of the immune system and failures in autophagic processes have been implicated in neurodegeneration. As such, dysregulation of autophagy may play a role in the pathophysiology of MS. Recent evidence suggests that Simvastatin (a HMG-CoA reductase inhibitor) induces autophagy in a variety of mammalian cells, and there is growing interest in the therapeutic potential of statins in the treatment of MS. Following promising results from a phase 2 trial, a phase 3 trial of Simvastatin treatment in secondary progressive MS is due to be conducted.

**Objective:** To evaluate the autophagy-modulating effects of Simvastatin in a variety of cell types, using flow cytometry.

**Methods:** LC3B immunofluorescence labelling was used to measure autophagy in Simvastatin-treated K562 (human erythroleukaemia cells) and Jurkat cells (human acute T cell leukaemia), as well as PC12 cells (rat neuroblastic cells). PC12 cells resemble neuronal cells when differentiated with nerve growth factor. Fluorescent labelling of organelles was used to analyse organelle-specific autophagic processes in mitochondria and lysosomes, and a Proteostat assay detected protein aggregation in PC12 cells. Two time points were analysed: 24 and 48 hours.

**Results:** Simvastatin induced autophagy in a dose-dependent manner in Jurkat (at 24h;  $p < 0.05$ ) and K562 cells (at 48h;  $p < 0.05$ ) treated at the following concentrations: 0  $\mu$ M, 0.1  $\mu$ M, 1  $\mu$ M and 10  $\mu$ M. The greatest upregulation of LC3B expression was seen at 1  $\mu$ M Simvastatin in both Jurkat ( $p=0.032$ ) and K562

( $p=0.0432$ ) cells. Simvastatin-treatment also slightly upregulated mitochondrial mass in Jurkat and K562 cells; increased lysosome expression in K562 cells, and upregulated LC3B and Proteostat expression in PC12 cells at 48 hours.

**Conclusion:** These preliminary findings suggest that Simvastatin influences autophagy, and this could be one mechanism by which Simvastatin may have therapeutic potential in the treatment of neurodegenerative diseases, such as MS. Further investigation is merited.

#### Disclosure

E James: Nothing to disclose

P Dua: Nothing to disclose

G Warnes: Nothing to disclose

UC Meier: Nothing to disclose

### EP1509

#### Axonal damage and motor impairment correlate with glial cell senescence in a model of multiple sclerosis

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**Background:** Cell senescence (CS) is an age-dependent process, promoted by a number of factors including oxidative stress and chronic inflammation. Typically, senescent cells undergo a number of changes such as division arrest and pro-inflammatory cytokine production. CS is thought to prevent damaged cells from becoming neoplastic, but evidence suggests that accelerated CS also contributes to loss of function associated with aging and neurodegenerative disease. The mechanisms that drive disability in the progressive forms of MS are not fully understood but age-related neurodegenerative processes are thought to play a key role.

**Aim:** To test the hypothesis that axonal damage and motor impairment in chronic demyelinating disease are associated with glial cell senescence.

**Methods:** We used the cuprizone model of demyelination in C57BL/6 mice. Immunohistochemistry for MBP, Iba-1 GFAP, APP were used to quantify demyelination, microglial/macrophage activation, astrogliosis and acute axonal damage, respectively.  $\gamma$ H2AX was used as a marker of DNA damage response (DDR). Senescent glial cells were detected with senescence-associated  $\beta$ -galactosidase (SA- $\beta$ -Gal) histochemistry and p16INK4A immunohistochemistry. The rotarod test and four-limb grip strength were used to assess motor performance.

**Results:** Chronic cuprizone feeding for 16 weeks led to callosal demyelination and astrogliosis with extensive acute axonal damage. In the corpus callosum of cuprizone-treated, but not naïve mice,  $\gamma$ H2AX immunohistochemistry was present in glial cell nuclei. There was also a significant increase in SA- $\beta$ -Gal and P16INK4A positive senescent glial cells in the corpus callosum, compared to naïve controls ( $P < 0.001$  and  $P < 0.05$ , respectively). Brain atrophy in cuprizone-treated mice was attested by decreased brain weight (8%,  $P < 0.001$ ), and performance using the rotarod test and four-limb grip strength ( $P < 0.01$ ), compared to naïve

controls. Correlation analysis revealed a significant association between the senescent glial cell load and four-limb grip strength ( $r_p = -0.867$ ,  $P < 0.01$ ), and between the senescent glial cell load and the extent of acute axonal damage ( $r_p = 0.92$ ,  $P < 0.01$ ).

**Conclusions:** Our study provides evidence of an association of axonal damage and motor impairment with the extent of glial cell senescence in a model of chronic demyelination. These data indicate that glial cell senescence might contribute to disability progression under conditions of chronic demyelination.

### Disclosure

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Professor Gorgoulis V: nothing to disclose

Dr Probert L: nothing to disclose

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### EP1510

#### Brain volume loss in neuromyelitis optica spectrum disorder

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There are few studies regarding brain volume loss in Neuromyelitis optica spectrum disorder (NMOSD) with contradictory results. Our aim was to describe longitudinally brain volume in a cohort of NMOSD patients compared to multiple sclerosis (MS) patients

**Methods:** Patients with diagnosis of NMOSD who had at least two MRI with a two year interval were included. MS patients matched by age and sex were included. SIENA and SIENAXr were used to measure brain volume.

**Results:** 20 NMOSD patients were included, 15 women (75%). Median age  $39 \pm 12$ . The first symptom was longitudinally extensive transverse myelitis (LETM) in 9 (45%), optic neuritis (ON) in 7 (35%), LETM plus ON in 1, brainstem in 1, cerebral in 1, brainstem plus LETM in 1. 9 patients (45%) were AQP4 positive. 43 matched MS patients were included. In the baseline analysis grey matter volume was significantly lower in the MS group  $0.55 \pm 0.1$  ( $\times 10^6$  mm<sup>3</sup>) compared to the NMO group  $0.66 \pm 0.08$  ( $p < 0.01$ ). Whole brain volume (WBV), whole white matter volume (WWMV), left thalamic volume (LTV), right thalamic volume (RTV) and brainstem volume (BV) was similar in both. In the two year follow-up percent brain volume change (PBVC) was significantly higher in the MS group  $-0.88 \pm 0.2$  (%) vs the NMO group  $-0.55 \pm 0.12$  ( $p < 0.01$ ). WBV was lower in the MS group  $1.5 \pm 0.1$  ( $\times 10^6$  mm<sup>3</sup>) vs  $1.6 \pm 0.13$  ( $p < 0.01$ ), GMV was also lower in the MS group  $0.51 \pm 0.11$  vs  $0.65 \pm 0.09$  ( $p < 0.01$ ) as LTV  $7 \pm 0.11$  vs  $7.5 \pm 0.4$

( $p < 0.01$ ). There was no difference between BV or WWMV between groups. In the two year follow-up of the NMO patients there was a significant reduction in the BV  $19.1 \pm 1.2$  (cm<sup>3</sup>) in baseline vs  $17.2 \pm 0.1$  in follow-up ( $p < 0.01$ ). There was no difference in the other variables.

**Conclusion:** MS patients showed significantly higher brain atrophy in baseline and follow-up. In NMOSD patients there was a significant reduction of brainstem volume in follow-up. These differences between groups may reflect different physiopathological mechanisms.

### Disclosure

nothing to disclose

### EP1511

#### Increased glutamate is the dominant cause of deep brain atrophy and multiple sclerosis severity

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**Objective:** In multiple sclerosis (MS), deep grey matter (DGM) atrophy has been recognised as a crucial component of the disease, presenting early and being associated with disability. Although the precise mechanism underlying grey matter atrophy is unknown, several hypotheses have been postulated. As our previous study found that hypothalamic alterations correlate with clinical outcomes, we decided to further test the hypothesis that hypothalamic metabolism is related to DGM atrophy.

**Methods:** We used 1H - Magnetic Resonance spectroscopy (1HMRS) of hypothalamus via 1.5T to test its metabolites in 26 patients with RRMS and 22 healthy age-matched controls. DGM atrophy was evaluated via the third ventricular widths (3VW) in T1 weighted MRI pictures. Metabolites of N-acetyl aspartate (NAA), Choline (Cho), Glutamate and Glutamine (Glx), myo-Inositol (mIns) and Creatine (Cr) and their ratios were correlated with Multiple Sclerosis Severity Scale (MSSS) and 3VW.

**Results:** In linear regression, for each log unit increase in 3VW, a 0.35 increase in MSSS was identified ( $P = 0.0039$ ); whereas for each log unit increase in Glx/NAA, a 0.93 increase in MSSS was identified ( $P = 0.090$ ).

**Conclusions:** In our study, we found that both NAA and Glx are associated with neurodegeneration of DGM, but Glx was found to be superior in determining both atrophy of DGM and disease burden.

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### Disclosure

Ema Kantorova, Hubert Poláček, Petra Hnilicová, Eva Baranovičová, Marián Grendár, Kamil Zelenák, Štefan Sivák, Vladimír Nosál, Dušan Dobrota, and Egon Kurča have nothing to disclose.

## Repairing mechanisms

### EP1512

#### Factors that regulate endogenous expression of the myelinating protein Gas6 in the brain

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Receptor tyrosine kinases of the TAM (Tyro3, Axl, Mer) subfamily are expressed in the CNS, and a number of reports have shown that their activation via their common ligand Gas6 has a positive effect on (re)myelination as well as on glial cell development. Gas6 undergoes post-translational processing, and thereby functional activation, through vitamin K (Vit K)-dependent gamma-carboxylation of a number of glutamic acid residues within the protein. However, little is currently known about the expression of Gas6 in the brain or the factors that regulate its expression and/or its post-translational activation state. Such knowledge can lend support to strategies aimed at activating Gas6-TAM signalling in the brain as a means of promoting remyelination in MS.

The study presented here is aimed at investigating the effects of various candidate molecules on the levels of endogenous Gas6 gene expression in the mouse brain. Molecules were administered *in vivo* or *in vitro* using an organotypic brain slice culture model. C57/BL6 mice were injected with Vit K1 intraperitoneally, and after 24 hours samples from brain and liver were harvested for gene and protein expression analyses. In addition, cultured brain slices from mice at postnatal day 8-12 were treated with the following agents: Vit K1, Vit K2, Vit D3, dexamethasone and IL-10. Samples were incubated with the tissues for four days, and tissues were analysed by qPCR for gene expression, and in addition the culture medium was assayed by ELISA for presence of released Gas6 protein. Results so far show that Vit D3 caused an increase in expression of the *gas6* gene in cultured mouse brain tissues. In addition, western blot analysis showed that *in vivo* administration of Vit K1 to mice caused an increase in the levels of gamma carboxylated proteins in the liver; brain analysis is ongoing.

These results show that Vit K administration can stimulate gamma-carboxylation of Vit K-dependent proteins *in vivo* and, furthermore, that the steroid hormone Vit D3 is able to upregulate Gas6 expression in brain tissue *in vitro*. Therefore, Vit D3 could be a potential promoter of remyelination during the course of MS through induction of endogenous Gas6-TAM signalling in the CNS.

#### Disclosure

Salman Goudarzi, Nadide Aydin, Sassan Hafizi: nothing to disclose

### EP1513

#### In vivo validation of chemical compounds with remyelinating potential

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**Background:** Remyelination occurs in patients with multiple sclerosis (MS), though it often fails or is incomplete. Therapies that favour endogenous oligodendrogenesis and promote remyelination may become attractive neuroprotective strategies for MS patients. In a previous study based on a Connectivity Map approach, we defined a gene expression signature of mature myelinating oligodendrocytes and identified five drugs (perhexiline, depropine, picrotoxinin, pimozone, valproic acid) with potential to enhance remyelination. Three out of the five drugs (depropine, pimozone, valproic acid) showed the ability to induce *in vitro* oligodendrocyte maturation in oligodendrocyte progenitor cells cultures, and were further selected for *in vivo* validation of their remyelinating potential in two animal models.

**Methods:** Experimental autoimmune encephalomyelitis (EAE) was induced in C57BL/6J mice with MOG<sub>35-55</sub> peptide. At day 12 post-immunization, once the EAE clinical signs were detected, animals were randomized and treated with the compounds for 21 days. A lysolecithin mouse model was induced by injecting lysolecithin in the spinal cord. Animals were randomized and treated for 10 or 24 days. Depropine, pimozone, valproic acid or vehicle (DMSO) were administered intraperitoneally daily to both mouse models. Spinal cords were removed and sectioned for immunostaining with MBP and Olig2. The demyelinated lesion area was measured and Olig2+ cell density assessed.

**Results:** Administration of selected compounds in a therapeutic setting did not result in an improvement of the EAE clinical course, which was similar in mice treated with depropine, pimozone, valproic acid compared with the vehicle group. In the EAE model an autoimmune response against myelin is induced, which could mask a positive effect of the drugs on remyelination. In order to avoid the effect of the immune system, we also tested the selected compounds in a lysolecithin model in which focal demyelination is due to a secondary toxic effect in oligodendrocytes. In the lysolecithin model, we observed that the density of Olig2+ cells was comparable in all groups, albeit showing a tendency to slight increase in animals treated with valproic acid, although statistically not significant.

**Conclusions:** Although depropine, pimozone, valproic acid showed good remyelinating capacity *in vitro*, they failed to enhance remyelination in immune-mediated and toxic-induced demyelination experimental models.

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CC, HP, HE, CM and CE declare no competing financial interests. XM has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis, Teva Pharmaceuticals and Almirall.

#### Founding source

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## Imaging

### EP1514

#### Classifying multiple sclerosis lesions with T1-weighted MR and myelin imaging

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**Introduction:** Myelin imaging is a potential tool to parse differences in focal myelin loss in T1 isointense and hypointense Multiple Sclerosis (MS) lesions. Since conventional magnetic resonance imaging (MRI) is unspecific to myelin we applied the *in vivo* whole-brain myelin imaging technique *multi-component Driven Equilibrium Single Pulse Observation of T1 and T2* (mcDESPOT) that allowed the evaluation of relative myelination by means of measuring the volume fraction of myelin water (VFM), a parameter related to brain white matter (WM) myelination<sup>1</sup>.

**Purpose:** To investigate the variation in VFM in individual FLAIR hyperintense MS lesions which are either isointense or hypointense to WM in T1-weighted images.

**Methods:** MRI data of 12 clinically isolated syndrome (CIS) patients were acquired at baseline and at 3, 6 and 12 months. T1-weighted and 3D-fluid attenuated inversion recovery (FLAIR) images were obtained and WM lesions were segmented as separate volumes of interest. VFM maps were derived using the established mcDESPOT processing method [1]. Selective lesion VFM read out enabled to address myelination differences in individual lesions. A matched control group was acquired. The significance of differences in VFM of T1 isointense and hypointense MS lesions was determined with an unpaired two-sided t-test ( $P < 0,05$ ).

**Results:** A total of 259 WM FLAIR lesions were examined, whereas 157 of them were isointense ( $VFM_{mean}=0,185$ ;  $VFM_{SD}=0,045$ ) and 102 hypointense ( $VFM_{median}=0,156$ ;  $VFM_{SD}=0,040$ ) on T1-weighted images. VFM in WM of healthy controls was 0,23. Significant differences ( $P=0,7*10^{-8}$ ) were found for the groups.

**Conclusion:** Lesions isointense to WM exhibited higher VFM values than lesions that were hypointense. Our findings demonstrate varying degrees of demyelination rejecting conventional MRI appearance in CIS/early MS.

#### References

- 1 Deoni et al., Magn Reson Med. 2008 Dec; 60(6):1372-87;

#### Disclosure

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### EP1515

#### Optimal timing of gadolinium-enhanced 3D FLAIR MRI for detection of leptomeningeal enhancement in multiple sclerosis

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**Background:** B-cell lymphoid aggregates have been implicated in meningeal inflammation, microglial activation, cortical grey matter demyelination, and disability progression in multiple sclerosis (MS) (1). Gadolinium-enhanced 3D-FLAIR (Gd-3D-FLAIR) MRI has recently been shown to identify foci of leptomeningeal enhancement (LME) in MS (2), thought to be an imaging biomarker for leptomeningeal inflammation. In order to determine disease modifying therapy (DMT) efficacy in controlling LME, it will be necessary to control for timing of image acquisition following gadolinium administration.

**Goals:** To identify the optimal timing of Gd-3D-FLAIR acquisition following gadolinium administration to identify LME in MS.

**Methods:** 8 foci of LME in 3 different MS patients were imaged by Gd-3D-FLAIR at 4 successive time points following injection spanning 4-45 minutes. Enhancement intensity was quantified by region-of-interest (ROI) measurements, averaged in sagittal and axial planes, with generation of time-intensity curves.

**Results:** Lesions were heterogeneous without definable optimal time for image acquisition. Mean time to peak enhancement = 23.8 min (standard deviation = 15 min, range 2-42 min). Rough guidelines for optimal timing of image acquisition suggest 10-25 min as reasonable parameters. Additionally, enhancement curves exhibited 3 different variations, remarkably similar to those described by Tofts (3): 3 lesions revealed prolonged wash-in curve; 2 lesions revealed slow wash-in/slow wash-out; and 3 lesions revealed rapid wash-in/rapid wash-out.

#### Conclusions:

- 1) While 10-25' post-injection acquisition seems appropriate, accurate assessment of DMT efficacy in modulating LME will require rigorous controlling of timing of image acquisition following gadolinium administration.
- 2) LMEs in MS are heterogeneous revealing 3 different types of wash-in/wash-out curves, suggesting a new avenue for investigation of DMT modulation of LME.

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1. Howell OW, Reeves CA, Nicholas R, et al. Meningeal inflammation is widespread and linked to cortical pathology in multiple sclerosis. *Brain* 2011; 134:2755-2771.
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## EP1516

### Supervised detection of newly appearing T2-w multiple sclerosis lesions with subtraction and deformation fields features

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**Background:** MRI has become one of the most important clinical tools for longitudinal analysis of multiple sclerosis (MS). Newly appearing lesions are indicative of the disease progression. Several automatic approaches have been proposed for the detection of newly appearing lesions, which can be classified as either supervised approaches that use intensity-derived features from the subtraction images or unsupervised approaches that use also deformation fields information.

**Aim:** We present here a supervised approach for detecting newly appearing MS lesions that combines both subtraction and deformation field features. Specifically, we use a logistic regression classifier trained with features from the baseline and follow-up intensities, subtraction values, and deformation field operators to provide a final segmentation.

**Materials and methods:** One year apart multi-channel brain MRI were scanned for 60 patients with a 3T magnet, including transverse T2-FLAIR, PD-w, T2-w and T1-w images. 36 of these patients presented new T2-w lesions that were semi-automatically annotated by expert neuroradiologists. The rest had no new lesions in the follow-up scans. All images were pre-processed and co-registered by multi resolution-multi stage affine registration, and a deformation field was also obtained using the Demons non-rigid registration algorithm.

**Results:** We performed a leave-one-out cross-validation strategy using the 36 patients with new T2-w lesions. In terms of detection, we obtained a 74.30% true positive fraction and 11.86% false positive fraction with a mean Dice similarity coefficient of 0.77. In terms of segmentation, we obtained a mean Dice coefficient of 0.56. We compared these results with those obtained with state-of-the-art methods such as Sweeney et al. (2013), Ganiler et al. (2014), and Cabezas et al. (2016), and our model had significantly better results ( $p < 0.05$ ). When testing the model with the 24 patients with no new T2-w lesions, only 5 false positives were found in 4 cases.

**Conclusion:** The proposed model decreases the number of false positives while increasing the number of true positives. The study also proves the benefits of using deformation field operators as features to train a supervised learning model. Our approach is simple and fully automated and reduces user interaction and inter- and intra-observer variability.

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## EP1517

### Spinal cord pathology and MS phenotypes - lesions, diffusion changes and spinal cord atrophy in 1036 multiple sclerosis patients

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**Background:** Abnormal MRI findings in spinal cord (SC) frequently occur in multiple sclerosis (MS). However, the relationship between lesions, diffuse pathology and SC atrophy in different MS phenotypes remains poorly understood.

**Objective:** To investigate spinal cord pathology in different MS phenotypes with 3T MRI.

**Methods:** We evaluated cervical and upper thoracic SC of 1,036 MS patients (739 women, 295 men) using the uniform MRI protocols: T2-weighted image with fat suppression (T2WI-Fat-Sat) in sagittal (slice thickness 2.0/0 mm) and 3D-T2WI-Fat-Sat in transversal plane 3D. There were 169 patients with clinically isolated syndrome (CIS), 743 relapse remitting (RRMS) patients and 124 secondary progressive MS (SPMS). The spinal cord volume (SCV) was measured semi automatically in 21 slices centered at intervertebral disc C3/C4. Lesion number and location (between craniocervical junction and vertebral body Th4) and presence of diffuse changes were evaluated by a neuroradiologist.

**Results:** Normally appearing SC was present in 33.7% (347 patients: CIS 45%, RRMS 33%, SPMS 19%). Diffuse abnormalities were present in 48 CIS (28%), 307 RRMS (41%) and 66 SPMS patients (54%). Focal lesions were described in 110 CIS (35%), 454 RRMS (39%) and 67 SPMS patients (54%). The mean of SCV (between vertebral body C3-C4): was 1.84 cm<sup>3</sup> (SD 0.18) in CIS, 1.76 cm<sup>3</sup> (SD 0.20) in RRMS and 1.64 cm<sup>3</sup> (SD 0.21) in SPMS. Statistically significant differences in SCV and type of SC pathology were found among all three groups ( $p < 0.001$ ) (adjusted for gender, age, disease duration). The maximum effect size was 0.15 for combination of diffuse changes and lesions and 0.14 for

whole diffuse changes. The mean of SCV differed significantly between men (1.83 cm<sup>3</sup>) and women (1.74 cm<sup>3</sup>). Interestingly, this effect declined with disability and men with SPMS had even smaller SCV (1.63 cm<sup>3</sup>) than women with SPMS (1.64 cm<sup>3</sup>).

**Conclusions:** This large dataset of 3T MRI derived from an academic MS clinic represents well a variety of SC abnormalities present in different MS phenotypes. Incidence of diffuse abnormalities in spinal cord on MR increases with severity of the disease. Diffuse abnormalities may be an important discriminator between disease phenotypes, which should be evaluated in longitudinal studies. In SPMS, SC atrophy was more pronounced in men, suggesting sex differences in pathophysiology of SCV loss.

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### EP1518

#### Periventricular lesions and 2016 MAGNIMS criteria for dissemination in space in patients with clinically isolated syndromes

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**Background:** The Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) group recently proposed new

dissemination in space (DIS) criteria that include lesions in the optic nerve, cortex and symptomatic region. In addition, these new magnetic resonance imaging (MRI) criteria for DIS raised the number of periventricular (PV) lesions from 1 to 3. We aim to investigate the performance of  $\geq 1$ ,  $\geq 2$  and  $\geq 3$  PV lesions in the 2016 MAGNIMS DIS criteria in predicting the conversion to clinically definite multiple sclerosis (CDMS) in patients with clinically isolated syndromes (CIS).

**Method:** Inclusion criteria:

- 1) CIS suggestive of central nervous system demyelination (since 2008);
- 2) clinical assessment and baseline brain MRI within 6 months of CIS onset;
- 3) spinal cord MRI available if patients presented with spinal cord syndrome; and
- 4) clinical follow-up of at least 24 months.

**Results:** We studied 161 CIS patients, 113 (70.2%) women, with a mean age at onset of 34 years. After a mean follow-up of 58 months, 102 (63.4%) patients were diagnosed as having MS according to the McDonald 2010 criteria. Seventy-eight (48.4%) patients converted to CDMS after a mean of 33 months from CIS onset, despite 46 (45%) patients underwent disease-modifying treatment (DMT) before the second clinical event. The sensitivity, specificity, and positive and negative predictive values of original 2016 MAGNIMS criteria requiring  $\geq 3$  PV lesions were 75.6%, 56.6%, 62.1%, and 71.2%; those for 2016 MAGNIMS criteria requiring  $\geq 2$  PV were 80.7%, 56.6%, 63.3%, and 75.6%; and finally, those for 2016 MAGNIMS criteria requiring  $\geq 1$  PV were 85.8%, 51.8%, 62.6% and 79.6%.

**Conclusions:** 2016 MAGNIMS DIS criteria requiring  $\geq 1$  PV lesion had a higher sensitivity but lower specificity than requiring  $\geq 2$  or  $\geq 3$  PV lesions. We found that the best combination of specificity and sensitivity for CDMS was seen for  $\geq 2$  PV lesions using MAGNIMS 2016 criteria. Because DMT can delay or prevent the conversion to CDMS, the high proportion of patients that underwent these therapies before a second attack, would explain the specificity values obtained.

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### EP1519

#### Iron deposition and volumes determination of subcortical, cerebellar and brain stem deep gray matter in multiple sclerosis: correlations

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**Background:** Increased iron deposition in subcortical deep gray matter structures is explained by the blood-brain barrier dysfunction, decreased iron clearance induced by axonal degeneration and inflammation or dysfunction of iron transport proteins induced by inflammation. Atrophy of the thalamus and basal ganglia nuclei have been established in multiple sclerosis, but the correlation between iron deposition and the loss of volume of the deep gray matter is limited studied. The aim of this study was to determine the presence of iron deposition and determinate the volumetric measurements in subcortical, cerebellar and brain stem deep gray matter structures in Multiple sclerosis, to compare them with the healthy control subjects.

**Methods:** Sixteen MS patients (9 RRMS and 7 SPMS), 8 CIS and 17 age- and sex-matched control subjects were included in this study. Region of interest (ROI) analysis on T2\* relaxation time maps was used to estimate T2\* values for deep grey structures. Regionas were manually outlined for head of nucleus caudatus, putamen, globus pallidus, pulvinar nucleus, remaining structure of thalamus, subthalamic nucleus, nucleus dentatus, nucleus fastigii, substantia nigra, and red nucleus and values averaged for left and right. The volumes of all these deep gray matter structures were also measured.

**Results:** Trends for T2\* relaxation times were reduced going from healthy controls to CIS and then to RRMS; however the T2\* values increased in SPMS relative to RRMS. Statistically significant differences were identified for MS patients less than healthy controls in left putamen ( $p=0,015$ ), left red nucleus ( $p=0,006$ ), left remaining thalamus ( $p=0,032$ ), right putamen ( $p=0,002$ ) and sple-nium ( $p=0,010$ ). There was no any correlation between T2 star and volumes values in all anatomic structures  $p>0,05$ ).

**Conclusions:** This study suggests the increased iron deposition as indicated by decreased T2\* relaxation times in subcortical and brain stem deep gray matter structures in Multiple Sclerosis as of the early stage of the disease. However, increased T2\* from RRMS to SPMS may reflect the influence of neuronal loss.

## Disclosure

Belgin Kocer: nothing to disclose

## EP1520

### Normative data of MRI-derived hippocampal volume from a large dataset of healthy subjects

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**Background:** Hippocampal atrophy occurs in Multiple Sclerosis (MS) patients since the early disease stages and has been associated with the impairment of episodic, visuospatial and verbal memory. Despite the growing clinical interest, Magnetic Resonance Imaging (MRI) derived measures of the hippocampal volume (HipV) from large datasets are missing, with important limitations for the implementation of this measure in large clinical studies.

**Objective:** To assess normative data of the HipV in healthy subjects (HS) on a large cross-sectional MRI dataset to be used as a reference in clinical studies.

**Materials:** The HipV of 727 HS was assessed from freely available MRI datasets. The age at scan-time ranged from 20 to 80

years. Data were stratified for gender and magnetic field strength (1.5 and 3 T). Volumes were obtained using a semi-automated approach, based on the manual editing of the masks obtained with FIRST (fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST). In 100 MRI scans, the accuracy of the method was compared with a fully manual segmentation output and with the fully automated outputs from FIRST and FreeSurfer. Finally, a multivariate regression using HipV corrected for head size as dependent variable and gender and age and their interactions as predictors was performed.

**Results:** Volume masks from our semi-automated approach were very similar to those obtained with the fully manual approach ( $7.1\pm0.7$  cm<sup>3</sup> vs  $7.1\pm0.6$  cm<sup>3</sup>,  $p=0.98$ ; DICE=0.92) and significantly lower than those obtained fully automatically with FreeSurfer ( $8.5\pm0.94$  cm<sup>3</sup>,  $p<0.001$ ; DICE=0.8) and FIRST ( $8.2\pm0.83$  cm<sup>3</sup>,  $p<0.001$ ; DICE=0.88). Age, quadratic age and gender were the predictors better fitting HipVs ( $R^2=0.164$ ,  $p<0.001$ ). Due to the dependence on gender, females showed constantly larger HipV with respect to males ( $0.44$  cm<sup>3</sup>,  $p<0.0001$ ). Due to the dependence on age, HipV decreased by 0.07% per year between 25 and 55 years of age (Hip female at 25 years:  $9.9$  cm<sup>3</sup>; at 55 years:  $9.7$  cm<sup>3</sup>), with an apparent acceleration (0.51% per year) between 55 and 85 years of age (Hip female at 85 years:  $8.2$  cm<sup>3</sup>).

**Discussion:** The study provides normative data of HipV over the adult life-span for males and females to be used as reference in MS studies at group and individual levels.

## Disclosure

L. Luchetti, G. Gentile, M. Battaglini, A. Giorgio have nothing to declare

N. De Stefano has received honoraria from Biogen-Idec, Genzyme, Merck Serono, Novartis, Roche and Teva for consulting services, speaking and travel support. He serves on advisory boards for Merck Serono, Novartis, Biogen-Idec, Roche, and Genzyme, he has received research grant support from the Italian MS Society.

## EP1521

### Accelerated myelin water imaging for assessment of cervical spinal cord demyelination in multiple sclerosis and neuromyelitis optica spectrum disorder

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**Introduction:** Myelin water fraction (MWF) is an imaging biomarker for myelin, acquired by an advanced MRI technique known as myelin water imaging (MWI) and traditionally derived using a lengthy multi-echo T2 sequence. Spinal cord (SC) application of MWI has been hindered by difficulties intrinsic to cord imaging. GRASE, a MWI acquisition technique accelerated by a factor of 3, has recently been implemented with high resolution and low acquisition time in healthy and injured SC.

**Objective:** Investigate the myelin content in the cervical SC of patients with multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) using GRASE MWI.

**Methods:** GRASE data centred at the C2/C3 disk level was collected from 8 healthy controls and 4 patients (1 relapsing-remitting MS (RRMS, EDSS=2.0); 1 primary-progressive MS (PPMS, EDSS=6.0); 2 NMOSD (EDSS=2.0 and 1.0)). Conventional anatomical MRI images facilitated analysis of MWF within regions of interest (ROI): whole cord (WC), white matter (WM), gray matter (GM), dorsal column (DC) and lateral funiculi (LF). Due to the exploratory, case study nature of the project, MWF results differing by >1 standard deviation ( $\sigma$ ) from HC mean were termed either high or low.

**Results:** Two patients had cervical SC lesions in the MWI field of view; RRMS had a small eccentric cord lesion and one of the NMOSD had a large transverse myelitis (TM) lesion. HC showed MWF variations between ROIs and agreement with literature (WC mean/ $\sigma$ =24.3/1.9%, WM=26.4/1.9%, GM=16.0/2.5%, DC=28.2/2.5%, LF=25.4/1.8%). NMOSD #1 with TM had drastically reduced MWF in all ROIs (WC=12.8, WM=14.0, GM=6.3, DC=6.9, LF=16.0%). NMOSD #2 had low MWF in all ROIs except the LF (WC=22.1, WM=23.9, GM=12.7, DC=24.1, LF=24.5%) despite lack of lesions. The MWF for the RRMS patient was similar to HC in WC, WM and GM ROI (WC=24.4, WM=25.9, GM=17.5%), but high in the DC (DC=31.0%) and low in the LF corresponding to lesion location (LF=23.1%). MWF values for the PPMS patient were similar to HC in all ROI (WC=25.1, WM=27.4, GM=16.8, DC=29.3, LF=25.5%).

**Conclusion:** GRASE MWI characterized healthy SC myelin content in agreement with literature values, and demonstrated reduced myelin water in TM lesion tissue. MWF values were reduced in NMOSD, regardless of visible lesions on conventional MRI, and suggested focal demyelination in RRMS lesion. These results support the clinical feasibility of using GRASE SC MWI as a potential quantitative measure of disease related myelin changes.

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## EP1522

### Demographic analysis and lesion characterization of leptomeningeal enhancement in multiple sclerosis

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**Background:** B-cell lymphoid aggregates have been implicated in meningeal inflammation, cortical grey matter demyelination, and disability progression in multiple sclerosis (MS) (1). Gadolinium-enhanced 3D-FLAIR (Gd-3D-FLAIR) MRI has recently been shown to identify foci of leptomeningeal enhancement (LME) in MS (2), thought to be an imaging biomarker for leptomeningeal inflammation. Awareness of demographics and lesion characteristics will facilitate determining if LME is a potential biomarker for anti-B cell therapies.

**Goals:** To analyze LME in MS patients in community-based practice by determining demographic and lesion characteristics, including relative frequency of LME by MS-subtype and disease modifying therapy (DMT), and correlation with disease activity.

**Methods:** MRI exams in MS patients showing LME were reviewed for demographics, disease subtype, and DMT, and lesions were analyzed for concurrent disease activity, location and morphology, and stability over time.

**Results:** 18 MS patients revealed 34 LMEs (mean 1.9, range 1-4), including 15 (83%) with relapsing remitting (RR), and 3 (17%) with secondary progressive (SP) MS. LME was seen with various DMTs and in patients receiving no treatment. 1 patient had imaging signs of active disease. Lesions were equally distributed between right and left, with 9 frontal, 13 parietal, 8 occipital, 3 temporal, and 1 cingulate lesions. Lesion morphology showed 11 rounded dots, 21 curvilinear lesions, and 1 globular lesion. 7 patients had prior exams ranging from 6-21 months, with 1 patient revealing 1 new lesion over a 10 month follow up.

## Conclusions:

- 1) In the community outpatient setting, LME is more likely to be seen in RRMS.
- 2) LME can be seen with a variety of DMTs.
- 3) LME is generally stable and unrelated to white matter disease activity.

## References:

1. Howell OW, Reeves CA, Nicholas R, et al. Meningeal inflammation is widespread and linked to cortical pathology in multiple sclerosis. *Brain* 2011; 134:2755-2771.
2. Absinta M, Vuolo L, Rao A, et al. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. *Neurology* 2015; 85:18-28.

## Disclosure

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## EP1523

**Regional distribution of cortical and subcortical damage in CIS patients: a study of first-year changes with clinical, CSF and radiological correlations**

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**Background:** Grey matter (GM) damage is a well-known phenomenon in the early stages of multiple sclerosis (MS), but its specific spatial distribution, clinical and cerebrospinal fluid (CSF) correlates are not well known.

**Objective:** To evaluate the regional distribution of cortical and subcortical GM damage in patients with clinically isolated syndromes (CIS) and to investigate whether clinical, CSF and radiological features are associated with specific damage in certain GM regions, both at baseline and during the first year of follow-up.

**Materials and methods:** From an ongoing longitudinal CIS cohort 121 patients with 3T magnetic resonance imaging (MRI) scans performed at baseline (3 months) and follow-up (12 months) were included. The selected cohort was classified according to their clinical, CSF and radiological correlates as follows: (1) clinical topography as optic neuritis (ON)(n=53) or OTHER (n=68); (2) presence or absence of oligoclonal bands (OCB) (n=107) as OCB+ (n=56) or OCB- (n=51); (3) number of Barkhof criteria fulfilled at baseline MRI as 3-4 criteria fulfilled, named Barkhof High (BH) (n=37) or 0-1-2 criteria fulfilled, named Barkhof Low (BL) (n=84). The scans were analyzed using the longitudinal stream included in the FreeSurfer software package. Baseline values and yearly change rates for lobar cortical thickness as well as for volumes of relevant subcortical structures were compared between subgroups adjusting for age and gender; results were corrected for multiple comparisons.

**Results:** At baseline significant cortical thinning was observed in patients with BH compared to BL in the parietal and occipital lobes bilaterally, in the left lateral and medial temporal lobe, and in the left cingulum, whereas no significant differences were observed between the other subgroups. At baseline, OCB+ patients showed lower volumes in bilateral thalami compared to OCB-, and BH patients showed lower volumes in the left putamen and bilaterally in thalami and brainstem compared to BL patients; no differences were observed between ON and

**Conclusions:** The spatial distribution of cortical and subcortical damage is influenced by the clinical, CSF and radiological characteristics of CIS patients.

**Disclosure**

Nothing to disclose for the present work

## EP1524

**Does frequent MRI scanning improve accuracy of evaluation of brain atrophy in individual multiple sclerosis patients?**

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**Background:** A relatively high intra-individual variability of longitudinal MRI of brain volume loss measurements over time renders challenging its application to individual multiple sclerosis (MS) patients.

**Objective:** To investigate if frequent brain MRI monitoring can improve the accuracy in identifying abnormal brain volume loss in an individual patient.

**Methods:** 157 relapsing-remitting MS patients had 7 MRI scans over 12-months follow-up. Of these,

81 patients had 13 bimonthly MRI scans available over 24-months follow-up. All 1585 MRI scans were performed on the same 1.5-Tesla scanner using an identical scanning protocol. Volumetric analysis of brain volume loss was performed by validated ScanView and SIENA software. Linear regression analysis was used for estimation of annualized brain volume loss, with a value greater than 0.4% defined as the pathological cut-off. We compared proportions of patients with abnormal brain volume loss obtained by analysis of different number of MRI time-points.

**Results:** An analysis of 2 MRI scans (month 0 and 12) showed abnormal brain volume loss in 93 (59.2%) of patients. When 3 MRI scans were included (month 0, 6 and 12), we found only 1 (0.6%) false negative and 5 (3.2%) false positive results compared with the analysis of 2 MRI scans, used as a reference for assessment of abnormal brain volume loss. Analysis of 7 MRI time-points showed 10 (6.4%) false negative and 13 (8.3%) false positive results compared with analysis of 2 MRI time-points. Change in the predictive accuracy of abnormal brain volume loss between results obtained by analysis of 2 and 7 time-points was 14.6%. Our results were confirmed in 103 patients analyzed by SIENA software and in 81 patients re-baselined at 12 months. We found no significant differences in predictive accuracy, neither between clinically stable and active patients, nor between patients with greater or lower brain volume loss rates. Various cut-offs of pathological brain volume loss (-0.34% and -0.6%) with different specificity and sensitivity provided very similar results.

**Conclusions:** Identification of individual patients with abnormal brain volume loss based on assessment of two MRI time-points over 12 months is associated with only 10-20% accuracy change compared with bimonthly MRI scan monitoring. Increased number of brain MRI time-points has only a moderate effect on the potential improvement more accurately identifying abnormal brain volume loss in individual MS patients.

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## EP1525

### Comparison of methods for brain atrophy assessment in multiple sclerosis

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**Background:** Neurodegeneration, in particular of the grey matter (GM), is one of the pathological hallmarks of multiple sclerosis (MS) and it represents one of the target outcomes of current therapeutic strategies for these patients. Several software tools for GM and brain atrophy measurement on MRI are currently available.

**Aims:** The aim of this study was the comparison of different methods [Advanced Normalization Tools (ANTs) version 1.9, FSL-SIENAX/SIENA 5.0.1, Icometrix-MSmetrix 1.7, and SPM version 12] currently used for GM and brain atrophy estimation on MR images of MS patients.

**Methods:** The dataset arranged consisted of 3D-T1 and 3D-T2FLAIR sequences of in-house simulated data, healthy controls' longitudinal data, test and retest MRI of MS patients acquired at different MR scanner field strengths and manufacturers, and MS patients' longitudinal data (1 year follow-up). Cross-sectional and longitudinal GM and brain atrophy estimation were

tested for each software, with and without T1-hypointense lesion filling. Accuracy and precision between the pipelines were compared. Paired t-tests were used to statistically compare the different results.

**Results:** The mean accuracy in GM and brain volume estimation for each method was: ANTs=0.96-0.96, FSL-SIENAX=0.95-0.96, MSmetrix=0.87-0.89 and SPM=0.97-0.96. The mean error in GM and brain atrophy measure was respectively: ANTs=0.52-0.11%, FSL-SIENAX=0.11%, MSmetrix=0.16-0.15% and SPM=0.09-0.1%. Except for ANTs ( $p < 0.001$ ), all softwares showed significant precision in GM and brain volume estimation between scan and rescan on both 1.5T and 3T scanners ( $p > 0.05$ ). However, all methods showed significant differences ( $p < 0.05$ ) when comparing tissue volume measurements between 1.5T and 3T scanners, and, except for SPM pipeline, among 3T manufacturers. For longitudinal atrophy, only ANTs was sensitive to different manufacturers and field strength acquisitions. Lesion filling significantly influenced longitudinal assessment of GM and brain atrophy for ANTs ( $p < 0.05$ ), while for SPM and MSmetrix it only affected GM atrophy measure.

**Conclusions:** Accuracy and precision between available software were evaluated and compared for different settings. The results of this work could help in the selection of the suitable pipeline among the available ones, according to the need of the analysis framework (research center, clinical setting or clinical trial), privileging in one case high accuracy rather than high reliability or vice versa.

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N. de Stefano has received honoraria from Schering, Biogen Idec, Teva Pharmaceutical Industries, Novartis, Genzyme, and Merck Serono SA for consulting services, speaking, and travel support. He serves on advisory boards for Biogen Idec, Merck Serono SA, and Novartis.

A. Rovira serves on scientific advisory boards for Biogen Idec, Novartis, Genzyme, and OLEA Medical, has received speaker honoraria from Bayer HealthCare Pharmaceuticals, Genzyme, Bracco, Merck Serono, Teva Pharmaceutical Industries, OLEA Medical, Stendhal, Novartis, and Biogen Idec, and has research agreements with Siemens AG.

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J. Palace reports personal fees from Biogen Idec, Teva Pharmaceutical Industries, Merck Serono, Bayer Schering, Novartis, Chugai Pharma, Ono Pharmaceuticals Co, and CI consulting, and grants from Merck Serono, Bayer Schering, and Novartis.

M. Filippi is Editor-in-Chief of the Journal of Neurology; serves on a scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Merck-Serono, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla,

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## EP1526

### The cytoarchitectonic anterior-posterior subdivision of BA4 reveals different resting state networks suggestive of maladaptive mechanisms in MS

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**Background:** Cytoarchitectonically, Brodmann area 4 (BA4) has been subdivided into two sub-regions: Anterior (BA4a) and posterior (BA4p). fMRI studies have shown that each sub-region contributes to different functions: BA4p activity is modulated by attention, fine forces, and imagined forces, whereas BA4a is related to force production. What are the healthy functional connectivity (FC) rsfMRI network of BA4a and BA4p, and how are these networks modulated by pathologies such as MS?

**Methods:** 26 subjects (10 HS: 5F; mean (std) age 30 (3.65) yrs and 16 relapsing-remitting MS (RRMS) patients: 8F; mean (std) age 34 (2.13) yrs; median (range) 9-hole peg test (9-HPT)=20.8 (14.7-33.1) were assessed with fMRI whilst resting. Region of interest (ROI)-to-ROI connectivity matrices were calculated for each subject. The left (dominant) hemisphere BA4 sub-divisions were defined according to a cytoarchitectonic probability atlas. The whole brain grey-matter areas were used as target regions. At the second level, FC measures were calculated and compared at group level using ANOVA, one or two sample t-tests, as appropriate. ROIs' FC measures were then correlated with the 9-HPT. Results were corrected with an FDR ( $p < 0.05$ ).

#### Results:

1. Individual groups: Both sub-regions in both groups display different rsfMRI connectivity networks. In MS, the BA4p network includes additional areas (e.g. posterior cerebellum, visual and inferior frontal regions).
2. A direct comparison of the networks in both groups shows that both BA4a/p sub-regions in MS have reduced FC to the right hemisphere. In the left hemisphere, MS exhibit higher FC than HS in motor and associative areas.
3. In MS, exploring correlations of the FC with the 9-HPT showed: i) worse performance in the 9-HPT was associated with reduced FC of BA4a with the right anterior cerebellum and the thalamus; ii) worse 9-HPT performance

was also associated with greater FC of BA4a/p with the right hemisphere.

**Discussion:** The observation that BA4p is mainly connected to associative and higher order functional areas while BA4a is connected to motor-related areas supports previous findings. Also, the correlation of the FC with the 9-HPT indicates that the increased FC may be either an unsuccessful compensatory attempt or even a maladaptive mechanism of disease. Multi-modal protocols may enable the investigation of the pathophysiology of these changes, which could derive from axonal loss and demyelination, but also perfusion or synaptic activity impairment.

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## EP1527

### Lower arterial cross-sectional area of carotid and vertebral arteries and higher frequency of secondary neck vessels are associated with multiple sclerosis

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**Background:** Arterial and secondary neck vessel system characteristics of multiple sclerosis (MS) patients were not previously investigated.

**Objectives:** To examine the frequency of neck vessels and their cross-sectional areas (CSA, in mm<sup>2</sup>) between MS patients and healthy controls (HCs).

**Methods and materials:** In this study, 193 MS patients and 193 age- and sex-matched HCs underwent two-dimensional (2D) time-of-flight (TOF) angiography at 3T. The main arterial (carotid and vertebral), venous (internal jugular), and secondary neck vessels were examined at 4 separate cervical levels (C2/3, C4, C5/6 and C7/T1). The analysis of covariance (ANCOVA) adjusted for age, body-mass-index, smoking status, hypertension, and heart disease was used to compare the differences between MS patients and HCs.

**Results:** After controlling for all confounding factors, MS patients had significantly lower CSA of the carotid arteries at C2/3

( $p=0.03$ ), C5/6 ( $p=0.026$ ) and C7/T1 ( $p=0.005$ ) levels, as well as of vertebral arteries at C2/3 ( $p=0.02$ ), C4 ( $p=0.012$ ) and C7/T1 ( $p=0.006$ ) levels, compared to HCs. Higher frequency of secondary neck vessels was found at all 4 levels in MS patients: C2/3 (12.9 vs. 10,  $p<0.001$ ), C4 (9.1 vs. 7.5,  $p<0.001$ ), C5/6 (7.8 vs. 6.8,  $p=0.012$ ) and C7/T1 (8.8 vs. 6,  $p<0.001$ ). The total CSA of secondary neck vessels was also significantly lower at all 4 levels ( $p<0.03$ ). In a subgroup of subjects without cardiovascular risk factors ( $>70\%$  of the study sample), similar differences were found for arterial and secondary neck vessels between MS patients and HCs. No significant differences in the CSA of jugular veins was found between MS and HCs.

**Conclusion:** MS patients showed lower CSA of carotid and vertebral arteries and higher frequency of secondary neck vessels and their CSAs compared to HCs, independently of the presence of cardiovascular risk factors.

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## EP1528

### Correlation between cognitive dysfunction and the corpus callosum index, brain atrophy, lesion load in multiple sclerosis

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**Background:** Cognitive dysfunction is associated with brain atrophy in multiple sclerosis (MS). The brain and lesion volumetric measurements are time and resource consuming and they are still not available in routine practice. The corpus callosum index (CCI) is measured using conventional magnetic resonance imaging (MRI) and it may be a surrogate marker of brain atrophy in MS. However, no study evaluated the correlation between cognitive dysfunction and CCI.

**Objective:** To assess the correlation between the cognitive dysfunction and the CCI, brain and MS lesion volumes in MS.

**Methods:** This study was a cross-sectional, exploratory study with relapsing-remitting MS using clinical and neuropsychological

assessments and MRI scans using a GE 3T scanner. The CCI is calculated measuring anterior, medium and posterior segments of CC adjusted to its greatest anteroposterior diameter. Automated total and segmented brain volumetric measurements were performed with the FreeSurfer software. MS lesion load volume was calculated using FreeSurfer. The correlations were adjusted for age, disease duration and educational level as appropriate.

**Results:** Twenty-four patients were included. They were in their majority women (58.3%) and Caucasians (87.5%). The mean age was 28.8 (SD 7.9) years and the median disease duration was 17.5 months (IQR 7 - 79.5). The median EDSS score was 2.5 (range 0 - 5). The CCI correlated with the scores on the MS Functional Composite - MSFC ( $R=0.457$ ,  $p=0.037$ ). The CCI correlated with individual scores from 9-Hole Peg Test ( $R=-0.463$ ,  $p=0.030$ ), Paced Auditory Serial Addition Test - PASAT ( $R=0.461$ ,  $p=0.035$ ), but has no correlation with the Timed 25-Foot Walk test. The CCI correlated well with the corpus callosum volume - CCV ( $R=0.798$ ,  $p<0.001$ ), white matter fraction - WMF ( $R=0.615$ ,  $p<0.003$ ), brain parenchymal fraction - BPF ( $R=0.489$ ,  $p=0.024$ ) and MS lesions volume ( $R=-0.704$ ,  $p<0.001$ ). There were no correlations between the CCI and gray matter fraction, as well as with the Expanded Disability Status Scale scores.

**Conclusion:** The cognitive dysfunction tests requiring hand function and auditory processing correlates with the CCI. The CCI correlates with brain volumetric measurements (CCV, WMF, BPF) and MS lesion load. The CCI is a practical surrogate marker of neurodegeneration in patients with MS.

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## EP1529

### Pathophysiology of MS tremor: an fMRI study

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**Introduction:** Tremor is a disabling movement disorder in Multiple Sclerosis (MS) that has no effective treatment and poorly understood pathophysiology. Understanding the brain regions involved in MS tremor could advance treatment development.

**Aim:** To understand the functional brain abnormalities associated with upper limb tremor in MS.

**Methods:** Twenty-three MS patients with unilateral upper limb tremor (MST) and twenty MS patients without tremor (MSC) underwent 3T magnetic resonance imaging (MRI) (MPRAGE, DIR and task fMRI) and a clinical tremor assessment. Tremor was quantified using the Bain score (0 to 10) for overall severity, writing and Archimedes spiral drawing. Cerebellar function was quantified using the Scale for the assessment and rating of ataxia (SARA). The fMRI tasks included a 'brick-breaker' joystick game that aimed to isolate tremulous movement by contrasting two conditions: 'play' (playing the game) and 'move' (rhythmic left/right movement of joystick without game). Task fMRI was analysed using FSL FEAT. Lesions were automatically segmented using LST toolbox version 2.0.15 for SPM. Regions of interest (ROI) were identified from FEAT analyses for correlation with tremor scores. Statistical analyses were performed in SPSS.

**Results:** MST (47.6±12.9y, Expanded Disability Status Scale (EDSS) 4.1±1.7) and MSC (46.2±11.0y, EDSS 3.4±1.6) groups were well matched. MST showed significantly higher activation in 'play' vs 'watch' in the bilateral sensorimotor cortex compared to MSC. Furthermore, activation within bilateral sensorimotor cortex significantly correlated with Bain tremor severity ( $p < 0.001$ ), handwriting ( $p < 0.000$ ), Archimedes spiral ( $p < 0.000$ ), and SARA ( $p < 0.005$ ). Ipsilateral sensorimotor cortex activation correlated with lesion load ( $p < 0.010$ ).

**Conclusion:** This study demonstrates a strong involvement of the sensorimotor cortex in the pathophysiology of upper-limb tremor in MS.

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Frederique Boonstra has nothing to declare

Gustavo Noffs has nothing to declare

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## EP1530

### Quantum - Value and feasibility of standardised, quantitative MRI analyses of MS patients in routine clinical practice

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**Background:** Magnetic resonance imaging (MRI) analyses play a key role both in the diagnosis and in treatment monitoring of patients with multiple sclerosis (MS). While reliable, quantitative analyses of highly standardised MRIs are carried out in clinical trials, comparable standards are yet to be implemented in clinical routine.

**Aim:** The data collection QUANTUM aims to evaluate if access to standardised quantification of MRI data and visualisation in reports, in addition to radiological findings provides additional benefit for neurologists working in day-to-day MS patient management.

**Methods:** Approximately 3,000 MRI analyses will be performed in 200 participating centres in Germany. The standardised MRI data (3D T1 gradient-echo sequence and 2D/3D FLAIR) are analysed by means of a centralised automatic processing pipeline (Biometrica MS®, jung diagnostics GmbH). The analysis comprises of a volumetric quantification of brain volume, as well as T2 lesion load and number. Percentage brain volume change is computed (using optimized SIENA pipeline) after the availability of follow-up scans. Scanner specific effects are accounted for using normative data sets for healthy controls generated for each individual MRI platform. The results are visualised and provided to the participating physicians as a report. The value and feasibility are evaluated using a questionnaire.

**Results:** QUANTUM started in June 2016. 60 radiological centres across Germany built-up scanner-specific data sets of healthy controls. By mid-2017, approximately 100 neurological centres would participate in the project and up to 1,000 MRIs would be analysed. The design used in data collection, the MRI protocol, and details of the centralised processing pipeline as well as baseline data from the first 100 centres will be presented.

**Conclusion:** In the course of the QUANTUM study, standardised MRI and MRI evaluations that were previously restricted to the clinical trial setting or expert sites were broadly made available. The optimisation of MRI protocols, the correction for scanner effects by means of scanner-specific control data and visualised reports could help to overcome limitations of comparable but less systematic approaches in routine clinical MS care. In addition and when fully initiated, data collected in the context of QUANTUM carries unique potential to improve the quality of imaging data collected in so-called "real-world registries" in the future.

## Disclosure

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## EP1531

### Accuracy and reliability of manual versus automated thalamus segmentation in patients with MS

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**Background:** Atrophy of the thalamus in multiple sclerosis (MS) is associated with cognitive malfunctioning and disability progression. An accurate and reliable volumetric analysis of the thalamus is hampered by low contrast between the thalamus and surrounding tissue on T1 MR images.

**Methods:** We analysed 3D T1 images from two independent datasets. Dataset 1 contained 30 MS patients, scanned on a 3 Tesla Philips scanner. Dataset 2 was publicly available (Biberacher et al. 2016) and contained a single MS patient, scanned 5-6 times on 3 different MR scanners (GE, Philips, and Siemens) within a few weeks. Thalamus volumes were determined manually using the annotation tool itk-SNAP (www.itksnap.org), along with anatomical atlases and under the supervision of an expert neurologist. For automated thalamus segmentation, we used a previously published (Opfer et al. 2016) atlas based volumetry approach built on SPM12 (Statistical Parametric Mapping), and volumetry with FSL FIRST (FMRIB Software Library).

**Results:** In dataset 1 (mean age 33 years, 70% females) the mean thalamus volume was 11.5 ml, 14.3 ml, and 9.9 ml for SPM, FSL, and manual segmentation, respectively. Mean volumetric off-set was 1.6 ml between manual and SPM derived volumes, and 4.5 ml between manual and FSL. Manually derived volumes correlated slightly higher with SPM volumes ( $r=0.77$ ) than with FSL volumes ( $r=0.71$ , difference not significant).

For all repeated scans of the 29-year-old female in dataset 2, mean thalamus volumes were 9.2 ml (SPM), 11.2 ml (FSL) and 6.5 ml (manual). Coefficient of variance was highest for manual segmentations (8.1%, 3.2% and 3.3% for GE, Philips and Siemens), and similar for SPM (0.98%, 0.81% and 1.0% for GE, Philips and Siemens) and FSL volumes (1.3%, 0.84% and 1.2% for GE, Philips and Siemens). The mean off-set between manual and SPM derived volumes was 3.4 ml, 2.6 ml and 2.2 ml for GE, Philips, and Siemens data, respectively. The off-set between manual and

FSL derived volumes was 5.2 ml, 4.5 ml, and 4.3 ml (for GE, Philips, and Siemens).

**Conclusion:** In our study, SPM and FSL thalamus volumes were larger than manually derived volumes. For FSL, this has been shown previously in healthy controls. The off-set was similar in dataset 1 and 2, and largely independent of the scanner. SPM derived volumes were closer to manual volumes than volumes assessed by FSL. Manual segmentations had a higher variability in the test-retest data than automatically derived volumes.

## Disclosure

AC. Ostwaldt, R. Opfer, L. Spies and C. Egger report no conflicts of interest.

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## EP1532

### Impact of 3 Tesla MRI on lesion detection in clinically isolated syndrome: a MAGNIMS multicentre study

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**Background and purpose:** Increased signal-to-noise ratio has improved the image quality of 3 Tesla (T) MRI in comparison to 1.5T. This allows an improved detection of multiple sclerosis (MS) lesions. However, to date it remains unclear if this is clinically relevant in the diagnosis and follow-up of clinically isolated syndrome (CIS) suggestive of MS. The purpose of this multi-centre study was to investigate whether 3T MRI affects lesion detection and diagnosis in CIS.

**Materials and methods:** We recruited 66 CIS patients and 26 healthy controls in 6 European MS centres. All subjects received

baseline 1.5T and 3T brain and spinal cord MRI. Patients who had not converted to MS during follow-up also received brain MRIs at 3-6 months and at 12-15 months. The number of lesions per anatomical region was scored separately on 1.5T and 3T images by three raters in consensus and subsequently dissemination in space and time (DIS and DIT) were determined according to the 2010 revision of the McDonald criteria. Statistical analysis was performed using the Wilcoxon signed-rank test for continuous variables and the McNemar test for dichotomous outcomes in SPSS 22.0.

**Results:** Interim analysis of 32 patients (age 34.8±9.0 years) and 12 controls (age 36.2±8.1 years) showed a trend towards a difference in the total number of lesions per patient, with a mean number of lesions per patient of 12.8 on 1.5T and 14.4 on 3T ( $p=0.088$ ). This was mainly due to a significant difference in detection of periventricular lesions at baseline, with a mean per patient of 3.5 on 1.5T and 4.5 on 3T ( $p=0.018$ ). For healthy controls no significant difference was seen between the two field strengths. DIS and DIT, and with that the diagnoses of MS, were similar between 3T and 1.5T (DIS  $p=1.00$ , DIT  $p=0.625$ , MS  $p=0.375$ ). Full analysis will be presented.

**Conclusion:** We have extended previous findings obtained in single-centre studies by showing that 3T increases lesion detection in CIS suggestive of MS, but does not significantly influence the fulfilment of the criteria for DIS and DIT.

## Disclosure

**M.H., J.B., I.K., M.V., N.C., E.S., M.Am., J.L.** and **B.W.** have nothing to disclose.

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**J.K.** has accepted speaker and consultancy fees from Merck-Serono, Teva, Biogen, Genzyme, Roche and Novartis.

**C.O.-G.** received honoraria as speaker from Biogen-Idec, Bayer-Schering, Merck-Serono, Teva, Genzyme and Novartis.

**O.C.** serves as a consultant for Biogen, Roche, Teva, Genzyme, Novartis and GE Healthcare.

**C.G.** received fees as speaker for Bayer-Schering Pharma, Sanofi-Aventis, Genzyme, Biogen, Teva, Novartis and Merck-Serono, and received a grant for research by Teva.

**C.L.** holds an endowed professorship supported by the Novartis foundation, has received consulting and speaker's honoraria from Biogen-Idec, Bayer Schering, Novartis, Sanofi, Genzyme and TEVA, and has received research scientific grant support from Merck-Serono and Novartis.

**M.W.** serves as a consultant for Roche, Novartis and Biogen.

**F.B.** serves as a consultant for Bayer-Schering Pharma, Sanofi-Aventis, Genzyme, Biogen, Teva, Novartis, Roche, Synthon BV and Jansen Research.

## EP1533

**Comparison of MRI findings in progressive multifocal leukoencephalopathy among HIV-positive patients and patients treated by immunosuppressive drugs, natalizumab or rituximab**

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**Purpose:** Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by reactivation of the JC polyomavirus. PML is most frequently associated with AIDS and emerges as a complication of Natalizumab (NAT) treatment of multiple sclerosis (MS). MRI presentation differs between HIV-positive individuals and MS patients treated with NAT. Rituximab (RITUX), a monoclonal antibody currently used for hematological malignancies and autoimmune disorders, is also associated with a moderately increased risk of PML. We compare the MRI presentation of RITUX-associated PML to NAT or HIV-associated PML.

**Materials and methods:** Brain MRI exams from 29 patients with a definite PML diagnosis including 12 after NAT treatment, 7 after RITUX treatment and 10 HIV-positive patients were analyzed using the following key MRI features: aspect in T1/T2/DWI and T2\* weighted images, location of the lesion, enhancement, U fibers and cortex involvement.

**Results:** The three PML entities show hyperintensities on T2 weighted sequence with lesions affecting U fibers associated to low signal intensities in U fibers on T2\* weighted sequence. Only NAT-associated PML shows a punctuate microcystic appearance in or in proximity to the lesion with a potential involvement of the cortex on T2, T2\* and on diffusion weighted sequence and in some cases an early contrast enhancement. Similarly to HIV-associated PML, RITUX-associated PML shows a rim of hyperintensity on diffusion weighted sequence and no early enhancement. However, we observed no punctuate appearance and no cortex involvement.

**Conclusion:** Imaging features of RITUX-associated PML are different from those of NAT-associated PML and are close to those observed in HIV-associated PML. These differences may be due to the higher level of immunosuppression in HIV patients and patients treated with RITUX compared to patients treated with NAT.

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## EP1534

**Retinal vessel oxygen saturation in multiple sclerosis**

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**Introduction:** Optical coherence tomography studies have previously demonstrated structural retinal changes in patients with Multiple Sclerosis (MS). Retinal oximetry is a non-invasive measurement of retinal metabolism and studies have shown changes in retinal oxygen saturation in another central nervous system disease.

**Objective:** To compare oxygen saturation in retinal blood vessels in MS patients with or without optic neuritis (ON) and healthy controls.

**Method:** Oxygen saturation of hemoglobin was measured in retinal blood vessels, with spectrophotometric noninvasive retinal oximeter. 29 MS patients, 12 with and 17 without history of ON were compared to 24 healthy individuals in a case-control study.

**Results:** Retinal arteriolar oxygen saturation was significantly higher in MS patients compared to healthy controls ( $96.6 \pm 3.2\%$  vs.  $94.1 \pm 4.0\%$ ;  $p=0.02$ , mean $\pm$ SD). There was an increased retinal arteriolar oxygen saturation in MS patients without ON compared to healthy controls ( $96.6 \pm 2.7\%$  vs.  $94.1 \pm 4.0\%$ ;  $p=0.03$  mean $\pm$ SD) and a trend towards an increase in MS patients with ON compared to healthy controls ( $p=0.08$ ). Retinal oxygen saturation in retinal venules was not significantly increased in MS patients compared to healthy controls ( $60.2 \pm 5.4\%$  vs.  $57.9 \pm 5.8\%$ ;  $p=0.15$ , mean $\pm$ SD). There were no significant changes in retinal venule saturation between MS patients with ON ( $p=0.12$ ) or MS patients without ON ( $p=0.37$ ) compared to healthy controls. Retinal arteriovenous difference was not significantly changed in MS patients compared to healthy controls ( $36.4 \pm 5.5\%$  vs.  $36.2 \pm 4.4\%$ ;  $p=0.87$ ). There was no significant difference measured in retinal vessel saturation when MS patients with ON and without ON were compared.

**Conclusion:** These results show metabolic changes in MS patients compared to healthy cohort. If confirmed in prospective studies, non-invasive retinal oxygen imaging may be a promising biomarker for MS.

## Disclosure

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## EP1535

### Stratifying FLAIR-hyperintense white matter lesions in a pilot study of MS, CIS, dementia and concussion using magnetic susceptibility mapping

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**Background:** In multiple sclerosis (MS), FLAIR or T2 magnetic resonance images (MRI) are used to identify new white matter

hyperintensities (WMH) as an important measure of treatment efficacy. However, WMH detected with these techniques are pathologically non-specific and can appear independent of demyelinating processes due to hypertension or aging. Quantitative MRI may help to differentiate lesions that look identical on FLAIR but differ pathologically.

**Goal:** To investigate the magnetic susceptibility (QSM) and  $R_2^*$  of WMH in relapsing-remitting MS, clinically isolated syndrome (CIS), concussion (CC) and dementia (DEM).

**Methods:** 3T QSM MRI data, together with FLAIR or T2, were acquired in 3 patients each of the 4 cohorts. QSM and  $R_2^*$  were estimated from the phase and magnitude of multi-echo gradient scans. After Laplacian unwrapping and V-SHARP, QSM maps were created using in-house software.  $R_2^*$  maps were obtained by linear fitting to the logarithmic data. WMH were manually defined on registered FLAIR or T2 scans. To establish the lesion contrast (iso/hypo/hyper-intensity), peri-lesional WM masks were defined by mask-dilation and subtraction of the original mask. Average  $\Delta$ QSM- $\chi$  and  $\Delta R_2^*$  values for each WMH were assessed.

**Results:** 19/43/30 and 38 lesions were identified in CC, DEM, CIS and MS (median age=20/82/19/62yrs). QSM-hypointensities were present across disorders, with increasing hypointensity, reflective of iron loss, in CIS and MS lesions ( $\Delta\chi_{CC}=-5.3/\Delta\chi_{MS}=-18.7$ ppb).

CC-WMH presented as predominantly QSM-isointense (57.9%,  $\Delta\chi=-0.3$ ppb), in agreement with an inflammatory response, compared to DEM-WMH, which appeared equally iso- and hyperintense

(39.5% both,  $\Delta\chi=0.6/9.7$ ppb) in response to a dilation of perivascular spaces and the development of mild myelin pallor (Udaka 2002, *Ann NY Acad Sci*).

$R_2^*$ -hypointensities dominated DEM and MS (79%/84.2%,  $\Delta R_2^*=-4.6/-6.8$ Hz), confirming that MS lesions largely represent myelin and iron loss.

In contrast, iso- and hypointense WMH were similarly found in CC and CIS (42%/52%,  $\Delta R_2^*=-1.9/-3.7$ Hz; 48/51%,  $\Delta R_2^*=-0.5/-4.6$ Hz), suggestive of lesser damage and possibly greater capability to repair in these younger cohorts.

The majority of CIS and MS lesions was QSM-hyperintense (55% both,  $\Delta\chi=14.2/21.3$ ppb), in line with the presence of edema, axonal and myelin damage (Li 2016, *JMRI*).

**Conclusion:** With its sensitivity to microstructure, QSM differentiates MS lesions from other FLAIR-WMH, while the complementary, less-specific  $R_2^*$  is reduced in most WMH.

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David Li has received research funding from the Canadian Institute of Health Research and Multiple Sclerosis Society of

Canada. He is the Emeritus Director of the UBC MS/MRI Research Group which has been contracted to perform central analysis of MRI scans for therapeutic trials with Novartis, Perceptives, Roche and Sanofi-Aventis. The UBC MS/MRI Research Group has also received grant support for investigator-initiated independent studies from Genzyme, Merck-Serono, Novartis and Roche. He has acted as a consultant to Vertex Pharmaceuticals and served on the Data and Safety Advisory Board for Opexa Therapeutics and Scientific Advisory Boards for Adelphi Group, Celgene, Novartis and Roche. He has also given lectures which have been supported by non-restricted education grants from Teva, Novartis and Biogen.

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#### EP1536

##### **Myelin and total water content show similar distributions in neuromyelitis optica and multiple sclerosis lesions**

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**Purpose:** To use advanced magnetic resonance imaging (MRI) to determine whether neuromyelitis optica (NMO) brain lesions exhibit different distributions of myelin damage or water content compared to multiple sclerosis (MS).

**Introduction:** MS and NMO are distinct inflammatory diseases that are similar in clinical presentation. NMO and MS lesions can appear similar on conventional MRI. Aquaporin channels are primarily affected in NMO, thus water distributions may differ between diseases. Due to different mechanisms of inflammation, the patterns of demyelination may also diverge in NMO lesions compared to MS. An advanced MRI technique, multi-echo T2 relaxation imaging, was used to quantify the total water content (WC) and myelin (myelin water fraction (MWF)) in NMO and MS lesions.

**Methods:** Ten NMO (mean age: 42y, median EDSS: 2.5), 13 MS (41y, EDSS: 2.5), and 15 healthy controls (41y) underwent MRI on a Philips 3T scanner. The healthy control data was used to create normative 3D atlases of the means and standard deviations of WC and MWF. The atlases were used to calculate Z-score maps for each MS and NMO patient, indicating how many standard

deviations away from the mean each value is for an individual patient compared to controls. NMO and MS lesions were identified on conventional images by a radiologist. The areas within lesions were analysed on the Z-score maps and histogram analysis was performed.

**Results:** The histograms for WC and MWF Z-scores were visually similar for NMO (average of Z-score means: WC: +3.2; MWF: -0.8) and MS lesions (WC: +2.3; MWF: -1.2). There was no difference between NMO and MS average Z-scores for WC (Student's t-test) ( $p=0.30$ ) or MWF ( $p=0.31$ ). The distribution of values within lesions was visualized using heat maps. The WC values were distributed with higher values near the centre of the lesions, while the MWF values had lower values near the centre. This pattern held true for both diseases.

**Discussion:** While the pathophysiology of MS and NMO are different, the lesions appear to be very similar in terms of their WC and MWF values. WC was higher, while MWF was lower in lesions when compared to the same regions in healthy controls. The distribution of values within lesions was also similar, where there is higher WC and lower MWF towards the centre of a lesion. This suggests that there is less myelin in the middle of lesions compared to the periphery. Overall, our results show that NMO and MS lesions are similar in terms of WC and MWF.

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#### EP1537

##### **The corticospinal tract in relapsing-remitting multiple sclerosis: a pilot tractography and fixel-based MRI analysis at ultra high-field**

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Bastani<sup>4</sup>, L.E. Cofré Lizama<sup>4</sup>, M.P. Galea<sup>4</sup>, T.J. Kilpatrick<sup>1,3</sup>, J.O. Cleary<sup>1</sup>, S.C. Kolbe<sup>1,5</sup>

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**Background:** Multiple sclerosis (MS) is a progressive neurological disorder of the central nervous system associated with demyelination and axonal loss, leading to permanent disability. Mobility impairment is the most disabling symptom in MS. Changes to lower limb disability in MS are likely related to axonal damage in the corticospinal tract (CST), the main motor pathway. Using the high SNR afforded by ultrahigh field (7T) MRI, diffusion MRI can be acquired with spatial resolution approaching anatomical imaging, with high angular resolution, and within clinically feasible scan times (~10mins). This allows for analysis using higher order diffusion models such as constrained spherical deconvolution that can estimate the fibre orientation distribution (FOD) in each voxel, together with associated axonal damage markers such as fibre density (FD) and fibre cross-section (FC) that can be analysed using “fixel-based analysis”<sup>1</sup>.

**Objective:** This preliminary study aimed to compare the degree of CST degeneration (loss of FD and FC) to clinical motor disability.

**Methods:** Eleven relapsing-remitting MS patients (1 male and 10 females, 42 ± 12.4 years) were tested. All had minimal or no lower limb dysfunction (EDSS < 4, pyramidal and cerebellar Kurtzke's Functional System (KFS) ≤ 2).

Diffusion weighted MRI was acquired using 7T MRI and a simultaneous multi-slice 2D spin-echo EPI sequence<sup>2</sup> (TR=7000ms, TE=72.4ms, multiband factor=2, GRAPPA=3, slices=128, 1.24mm isotropic resolution, whole brain coverage, 3 b-shells: 1000, 2000, 3000 s/mm<sup>2</sup>, 103 directions, 6 b0 images).

FODs were estimated for each voxel for each subject using MRtrix 3.0, and a population FOD template was generated. Probabilistic tractography was used to identify the CST (Fig. 1). FC and FD were computed from the CST and compared to pyramidal KFS scores for each subject.

**Results:** Loss of FD (but not FC) in the subcortical white matter of the CST was associated with increased pyramidal dysfunction ( $p_{uncorrected} < 0.05$ ) (Fig. 2).

**Conclusion:** Using ultra-high field 7T diffusion MRI we detected loss of FD in the CST that was associated with pyramidal disability. FD could provide a useful marker of disease progression leading to loss of mobility. Future studies will aim to replicate this in a larger cohort.

**References:** 1. Raffelt, D.A. *et al. Neuroimage* 144,58-73 (2017) 2. Vu, A.T. *et al. Neuroimage* 122, 318-331 (2015)

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## EP1538

### MRI-based measures for quantifying treatment efficacy in multiple sclerosis

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**Background:** Magnetic resonance imaging (MRI) plays a key role in tracking disease activity, evaluating treatment efficacy, and predicting long-term disability in multiple sclerosis (MS) patients. Natalizumab (henceforth NA) has been shown to reduce the rate of clinical relapse compared to placebo and slow accumulation of new lesions that appear hyperintense on T2-weighted MRIs. It remains unknown whether NA has quantifiable effects on MRI lesional intensities that could be used as potential markers for therapeutic response or tissue repair.

**Objectives:** This study assessed differences in MRI intensity within new lesions appearing before and after NA initiation. Secondary objectives tested for intensity changes in chronic lesions that may reflect repair.

**Methods:** Relapsing remitting MS patients were retrospectively identified who initiated NA at the University of Pennsylvania between 2009-2014. Fluid attenuated inversion recovery (FLAIR) and T1-weighted sequences from two pre-NA scans and one post-NA scan were obtained from a common protocol and preprocessed. Manual segmentations identified chronic lesions, defined by their presence on earliest MRI (1.3 years before NA on average), and acute lesions, defined by first appearance on the MRI immediately prior to NA initiation (0.4 years before NA on average) or after NA initiation (0.6 years after on average). The mean and quartiles of normalized MRI intensities from 214 chronic and 229 acute lesions were analyzed using linear mixed models to estimate changes in lesional intensities after NA initiation.

**Results:** Although not statistically significant, mean (25th, 50th, 75th quartile) normalized FLAIR intensity decreased by 0.8 (0.5, 1.2, 1.1) units in post-NA new lesions compared to lesions that formed prior to NA, suggesting therapeutic response. Similarly, mean (25th, 50th, 75th quartile) normalized T1 lesional intensity increased by 0.7 (1.0, 0.2, -0.2) units. In chronic lesions, mean (25th, 50th, 75th quartile) normalized FLAIR intensity decreased by 1.0 (0.6, 1.0, 1.2) units and mean (25th, 50th, 75th quartile) normalized T1 intensity increased by 1.4 (2.0, 1.5, 0.7) units, suggesting possible tissue repair after NA initiation.

**Conclusions:** Natalizumab may lead to decreases (increases) in normalized FLAIR (T1) intensities in new lesions. Lesion-based



analyses may provide a useful measure of treatment efficacy. Further investigation using a larger study cohort is warranted.

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## EP1539

### Time resolved MR angiography in patients with multiple sclerosis, their healthy siblings and unrelated controls

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**Purpose:** Our aim was to use a novel time-resolved magnetic resonance (MR) technique, for high contrast enhanced venography with high temporal resolution, as an objective method for the assessment of cerebral venous hemodynamics in patients with multiple sclerosis (MS), their healthy siblings, and unrelated healthy controls.

**Materials and methods:** 39 patients with clinically definite MS, 31 siblings and 31 unrelated controls were recruited and imaged between January and December 2011. Dynamic magnetic resonance angiography data were acquired using 4D-TRAK on a 3T Philips Achieva scanner. Two blinded readers assessed contrast arrival times over 68 time points while reviewing the upper and lower cross sections of the carotid arteries and the internal jugular veins (IJV) for maximum contrast. We further computed the cerebral circulation times (CCT) as the arrival time to the IJV minus the arrival time to the arteries based on the two manually defined landmarks. Statistical analysis was done using Kruskal-Wallis and ANCOVA, taking the age as a covariant.

**Results:** The median left and right CCTs were 6.14s for patients, 6.24s for siblings, and 6.14s for unrelated controls for the upper landmarks and 7.80s for patients, 7.60s for siblings, and 7.80s for unrelated controls for the lower landmark. No significant differences in the CCTs were found between the three groups ( $p > 0.2$ ). Furthermore, no correlations were found between the CCTs and the brain volumes, expanded disability status scale (EDSS) or disease duration.

**Conclusion:** The lack of significant differences in venous flow between patients with MS, their siblings and unrelated controls on MR venography suggests that flow abnormalities are not characteristic for MS. Our results directly contradict previous findings

obtained using ultrasound but agree with results obtained with catheter venography.

## Disclosure

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**Lindsay Machan** is a member of the Research Steering Committee for Cook Inc and Medical Advisory Board for Boston Scientific Corp.

**Dessa Sadovnick** has received personal compensation for activities with Biogen Idec, Merck Serono, Teva Neuroscience, and Bayer Pharmaceuticals Corp as a speaker.

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## EP1540

### Functional brain network stability in natalizumab treated multiple sclerosis patients: a one year follow-up study

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**Introduction:** Natalizumab treatment is highly effective in limiting the formation of new white matter (WM) lesions in multiple sclerosis (MS). It is currently unknown, however, in which way natalizumab influences the functional brain network. In this study, we longitudinally examined the severity of functional network changes in MS patients treated by either interferon- $\beta$ /glatiramer acetate (IFNb/GA) or natalizumab over a period of one year.

**Methods:** For a period of one year, we followed relapsing-remitting MS patients initiating natalizumab at baseline (N=20), continuing IFnB/GA (N=17) and healthy controls (HC; N=13). All participants underwent resting-state fMRI and structural MRI, as well as cognitive and clinical assessments. For each subject, a whole-brain functional network was constructed by calculating the functional connectivity between all pairs of brain regions in the automated anatomical labeling (AAL) atlas. For each network

connection a Z-score was calculated relative to HC and the average increase or decrease in Z-scores at baseline and after one year were defined as the severity of functional network change. Progression in severity of functional network changes was related to lesion load, whole-brain WM integrity and deep grey matter volume, as well as longitudinal changes in average cognition, nine-hole peg test (9-HPT) performance and EDSS.

**Results:** At baseline, only significant increases in connectivity were observed in MS compared to HC ( $p < 0.05$ ), without differences between the natalizumab and IFNb/GA groups. After one year, functional connectivity levels further increased, but only in patients treated with IFNb/GA (24%;  $p < 0.05$ ), whereas functional connectivity levels remained stable in the natalizumab and HC group. In MS, this change in functional connectivity was associated with increasing lesion load and loss of WM integrity (resp.  $\rho = 0.408$  and  $\rho = -0.383$ ) and a decline in performance on the 9-HPT ( $\rho = 0.419$ ).

**Conclusion:** In MS patients initiating natalizumab treatment, the severity of functional network changes remained stable in the first year of treatment, while the functional connectivity of those patients treated with IFNb/GA therapy increased over a 1-year period. These findings indicate that natalizumab may stabilize the functional network in MS.

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## EP1541

### Resting State in relapsing-remitting MS patients with verbal episodic memory or social cognition impairment and low level of motor disability

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**Background:** Functional MRI (fMRI) provides information about the plasticity of the human brain. Special interest has arisen from the study of cognitive impairment and Resting State (RS) fMRI in MS.

**Objective:** To investigate RS differences in MS patients with low level of motor disability with and without cognitive impairment and to correlate these findings with clinical and neuropsychological measures.

**Methods:** Cross-sectional study including RS fMRI and structural images (3D T1/FLAIR) acquired from a 3T scanner (Philips Ingenia). Clinical evaluations and a complete neuropsychological battery were also performed on the same day  $\pm$  2 weeks. Verbal Episodic Memory (VEM-California Verbal Learning Test VIII-CVLT) and Social Cognition (SOC-Mini Social and Emotional Assessment-miniSEA) were assessed creating groups (normalVEM vs. impairedVEM and normalSOC vs. impairedSOC) according to Z score with a cut-off  $\leq -1.5$ . RS studies were analysed with MELODIC/FSL. After concatenating all studies, RS networks were visually identified. Then, a dual regression analysis was performed to assess the differences between normalVEM vs. impairedVEM, and normalSOC vs. impairedSOC. Finally, the mean value for each subject in the clusters that showed significant differences ( $p < 0.05$  threshold free cluster enhancement images) was extracted to correlate with the clinical and neuropsychological measurements.

**Results:** We included 37 relapsing-remitting MS patients, 65% women, mean age  $36.2 \pm 9$  years, mean disease duration  $6.4 \pm 4$  years, median EDSS 1.0 (range 0 - 6). Verbal Episodic Memory was impaired in 45.9% and Social Cognition in 24.3%. RS showed significant differences (decreases and increases) in networks including sensory-motor, visual, executive, default network and cerebellum for both group comparisons. In addition, differences found in the VEM group comparison were correlated with CVLT Z score and EDSS (normalVEM median EDSS 1.0 vs. impairedVEM median EDSS 2.0,  $p = 0.04$ ); while differences found in the SOC group comparison, were correlated with miniSEA Z score. The direction and magnitude of the correlations were dependent on the region.

**Conclusion:** When MS patients were classified according to their VEM or SOC impairment, RS showed significant differences in brain synchronization. Interestingly, RS was sensitive to mild differences of EDSS in the VEM group. Results suggest that RS could reflect the cognitive status of MS patients within plausible neurocognitive networks.

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Álex Rovira serves on scientific advisory boards for Novartis, Sanofi-Genzyme, and OLEA Medical, has received speaker honoraria from Bayer, Sanofi-Genzyme, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, Novartis and Biogen Idec, and has research agreements with Siemens AG and Icometrix.

Deborah Pareto has nothing to disclose

## EP1542

### A deep-learning method for tissue volumetry from multi-spectral magnetic resonance imaging in multiple sclerosis

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We present a method (DeepSCAN-MS) for automated volumetry of healthy appearing and white-matter lesion tissue from multi-spectral magnetic resonance imaging in multiple sclerosis. The method, which is an application of deep learning, is trained on a combination of automated tissue classification and manual lesion delineation, and provides a method for tracking the two of the NEDA-4 biomarkers for disease activity. These biomarkers cannot be adequately tracked manually, either because they are infeasible (atrophy) or time consuming and non-repeatable (lesion load)

FLAIR imaging of 123 MS patients from the Inselspital were examined by two raters, who delineated the FLAIR hyperintense lesions on each axial slice. The delineations from the first rater were superimposed on segmentations obtained from FSL FAST (2) (showing WM, GM and CSF) and Freesurfer (subcortical grey matter). The fused segmentations from 80 randomly selected cases, together with the FLAIR, T1-weighted and T2-weighted images were, after rigid registration, used to train an ensemble of deep learning classifiers (variations on the recently introduced Densenet architecture) The method was then applied to the remaining 43 cases. Segmentations of intracranial volume, white matter, grey matter and lesion tissue were significantly correlated with ground truth volume ( $p < 0.001$ ) in each case. A Bayesian method for providing confidence intervals for volumes allows to track significant volume change over time.

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## EP1543

### 3T-PET/MRI discloses different metabolic states of cortical lesions in multiple sclerosis

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**Background:** Cortical lesions (CL) are believed to play a role in the accumulation of physical and cognitive disability in multiple sclerosis (MS). Up to date, no study has investigated the metabolic behavior of CL.

**Aim:** To analyze the absolute <sup>18</sup>F-FDG metabolism of CL in MS patients by means of a fully integrated 3T-Positron Emission Tomography/Magnetic Resonance Imaging (3T <sup>18</sup>F-PET/MRI) system.

**Methods:** Fifteen early relapsing remitting MS (eRRMS) with no sign of cognitive impairment (CI) and fifteen RRMS with significantly longer disease duration and clinical evidence of CI (CI-RRMS) were enrolled in the study. Physical and cognitive evaluations were done by EDSS and Rao's BRB. Dynamic <sup>18</sup>F-FDG-PET/MRI (Siemens Biograph 3TMRI/PET System) data were analyzed with Patlak plot method to obtain absolute metabolic rate of glucose (aMRglu). CL and white matter (WM) lesions were identified on 3D FLAIR and 3D DIR images, respectively.

**Results:** eRRMS had lower CL volume and number than CI-RRMS and, despite the limited number of patients, the differences were significant ( $p=0.02$  and  $p=0.01$ , respectively). The great majority of CL (68.0%) showed aMRglu values in the range of the surrounding apparently normal cortex, but 17.8% had significantly increased aMRglu values and 14.2% were hypometabolic. aMRglu inversely correlated with CL number and volume in both left ( $p=0.01$ ,  $r=-0.49$  and  $p=0.02$ ,  $r=-0.42$ ) and right parietal ( $p=0.02$ ,  $r=-0.43$  and  $p=0.03$ ,  $r=-0.39$ ) lobes.

**Interpretation:** CL were found to differ in aMRglu values. Whether the metabolic state of CL reflects their evolution from an initial hypermetabolic inflammatory phase (potentially excitotoxic) to a final hypo-metabolic neurodegenerative phase merits to be investigated. Indeed, the metabolism of CL might be the link between inflammation and neurodegeneration in MS.

## Disclosure

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#### EP1544

##### Neuropsychological correlations differ according to the spatial distribution of corpus callosum atrophy in multiple sclerosis

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**Introduction:** Corpus callosum (CC) measurements have been shown to correlate with brain volumes and disease severity in multiple sclerosis (MS). While most CC measurements are performed taking that structure as a whole, it is worth noting that the origin of the fiber across the CC segments is heterogeneous. This study was done to assess whether different spatial distributions of atrophy across the CC could be associated with impairment in specific parameters of disability and cognitive dysfunction in MS. **Methods:** Patients with relapsing-remitting MS underwent 3.0 T brain MRI. The FreeSurfer® software was used to estimate the CC volume, segmented by regions (anterior, mid-anterior, central, mid-posterior, and posterior). Clinical assessment included the Expanded Disability Status Scale (EDSS), the MS Functional Composite (MSFC), the Brief Repeatable Battery of Neuropsychological Tests, the Wechsler Memory Scale III (WMS), the Stroop test, and the Boston Naming Test (BNT).

**Results:** Twenty-one patients with relapsing-remitting MS were included. Moderate to strong correlations were seen between the PASAT (attention, working memory and information processing) and almost all of the CC segments ( $r=0.529$  to  $0.647$ ,  $p<0.01$ ), except the anterior one, as well as between the BNT (semantic memory) and the central, mid-posterior, and posterior segments of the CC ( $r=0.479$  to  $0.550$ ,  $p<0.03$ ). Only the mid-posterior CC correlated with tests of verbal memory, namely WNS - subtests Logical Memory I and II, and Free and Cued Selective Reminding Test - delayed recall ( $r=0.452$  to  $0.515$ ,  $p<0.04$ ). The anterior CC did not correlate with any tests. None of the CC segments correlated with EDSS, other MSFC subtests, or other neuropsychological tests.

**Conclusion:** In line with pathological and advanced MRI studies, this study with conventional MRI supports different patterns of neuropsychological dysfunction according to the topographic distribution of atrophy across the CC in patients with MS.

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#### EP1545

##### Comparison of automated brain atrophy and lesion volume quantification tools in multiple sclerosis patients

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**Introduction:** This study used the commonly available automated tools of SIENAX from FSL, Lesion Segmentation tool (LST) for SPM, and NeuroQuant including its lesion segmentation module LesionQuant, from CorTechs Labs, Inc. to determine lesion and brain volumes in a group of MS patients. These results were compared to expert manual lesion segmentations. SIENAX and LST are research tools, widely used in the research community. NeuroQuant is an FDA cleared, fully automated brain segmentation and volume measurement tool for clinical use.

**Methods:** T1-weighted and FLAIR images from 24 MS (19F, 5M,  $42 \pm 12$  yo) patients were included in the study. Total brain, gray matter and white matter volumes were measured using SIENAX and NeuroQuant. The lesion volumes were calculated using LST and the LesionQuant module of NeuroQuant. Lesions were also manually segmented for each patient. Manually determined lesion volumes were compared with the results of the automated tools. The Pearson correlation coefficient was used in comparing brain volume measurements of SIENAX and NeuroQuant, as well as comparing the lesion volumes from LST, LesionQuant and manual segmentation.

**Results:** The total brain volumes calculated with SIENAX and NeuroQuant were correlated ( $R=0.83$ ). LST and LesionQuant lesion volume determinations were highly correlated with each other and with manually determined lesion volumes (all  $R=0.97$ ).

**Conclusions:** The two automated lesion determination tools, LST and LesionQuant, have comparable performances and their results are highly correlated with the manually segmented lesion volumes. The whole brain volume determinations using SIENAX and NeuroQuant also produced results similar to each other and can be used to quantify brain atrophy in MS patients.

#### Disclosure

Authors are the employees of CorTechs Labs, Inc.

#### EP1546

##### A comparison of spinal cord grey and white matter atrophy in MS and healthy controls with clinical correlations

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**Background:** Several studies have indicated the relevance for multiple sclerosis (MS)-related disability of spinal cord grey matter atrophy, which can now be estimated using appropriate MRI sequences.

**Objective:** To further evaluate the feasibility and clinical relevance of MRI-derived estimations of spinal cord grey matter atrophy.

**Material and methods:** A convenience sample of MS patients and healthy controls (HC) was scanned using brain 3D T1w (MPRAGE) and T2-FLAIR, and spinal cord 2D heavily T1w (PSIR) sequences on a 3T magnet. MPRAGE and T2-FLAIR sequences were used to obtain whole brain parenchymal, grey and white matter fractions (BPF, GMF and WMF) using the automatic *Lesion Segmentation Tool* and filling implemented in *Statistical Parametric Mapping*. An experienced technician with neuroradiological supervision used a semiautomated method implemented in *JIM* software on MPRAGE sequences to obtain cord length, volume and mean area from medulla oblongata to C3 (CLmo, CVmo, CMAmo), and cord length and volume from C1 to C3 (CLc1, CVc1). PSIR sequences were used to obtain whole cord, grey and white matter areas (CMAc2, CGMA, CWMA) at C2-C3. Appropriate statistical tests were used before and after age-adjustment.

**Results:** 49 patients (32 female / mean age 43,0 years -SD:11.0- / median EDSS 4.0 - range: 0 - 7.5 / mean brain lesion volume 17,9 ml -SD:18,4-) and 13 HC (7 female / mean age 37,8 years -SD:9.7-) were included. CGMA and CWMA could only be reliably obtained in 17 patients and 12 controls mostly due to lesion-related segmentation difficulties. Before and after age adjustment, patients with MS had significantly lower BPF, WMF, CLmo, CVmo, CMAmo, CLc1, CVc1, CMAc2 and CGMA than HC. Significant negative associations with EDSS were observed for BPF, GMF, CVmo, CMAmo, CVc1, CMAc2 and CGMA, but only CMAmo (standardized beta coefficient (sbc)=-0,254; p=0,091), CVc1 (sbc=-0,244; p=0,072) and CMAc2 (sbc=-0,244; p=0,072) survived age-adjustment.

**Conclusion:** Due to lesion artefacts two thirds of patients cannot have their spinal cord grey matter areas reliably estimated but, in spite of lower sample sizes, significant findings can still be observed.

## Disclosure

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JC & MA have nothing to disclose

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## EP1547

### Magnetic resonance imaging in the NMO seropositive and seronegative for AQP4

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**OBJETIVE:** To describe the radiological characteristics of the NMO and to evaluate differences between the AQP4 positive and negative groups.

**Methods:** Patients with NMO (2006) followed between 1999 and 2015 at Hospital da Lagoa (RJ) who dosed anti-AQP4 by IFF and / or cellular methods, with at least two available skull and spinal MRI scans were selected for this study . The NMO complex syndromes (NMO-CS) criteria of 2015 were applied to these patients. The MRI analysis was performed by two specialists who investigated the typical radiological signs for NMO-CS. The frequency and characteristic of the lesions were compared in the serum positive and negative AQP4 groups.

**Results:** The 38 patients with NMO included in the study fulfilled the diagnostic criteria of NMO-CS (2015). The radiological criterion was filled with the initial MRI in 60% of the cases considering specific supratentorial, infratentorial lesions, in the optic nerve and medulla lesions. The most frequent lesions in the AQP4 positive patients in the order of frequency were: 1st - Cervical myelitis, 2nd - Bilateral or unilateral optic neuritis and 3rd - Brainstem lesions. In the negative AQP4 the order was: 1st - Dorsal myelitis, 2nd - Unilateral optic neuritis and 3rd - Brainstem lesions.

**Conclusion:** (1) The features found in the NMO were: extensive lesion of the optic nerve until the chiasm, Peri-chiasmatic regions and extensive atrophy of the optic nerve; Extensive longitudinal uni or bilateral lesion of the spinal cortical tract from the origin to the brainstem; Cervical myelitis with extension to the bulb and extensive atrophy of the spinal cord; Large coalescing lesions on the trunk and brainstem with ependymal lesions; Extensive lesions in the cerebral hemispheres in continuity with supratentorial ependymal lesions. (2) There was no significant difference in the brain lesions according to AQP4 status.

**Key words:** Optic neuromyelitis, Multiple sclerosis. Magnetic Resonance Imaging

## Disclosure

There is no conflict of interest.

## EP1548

### MRI in transverse myelitis: correlation with expanded disability status scale

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**Background:** Magnetic resonance imaging is used as a diagnostic tool to detect spinal cord lesions.

**Objective:** The objective of this paper is to examine cross-sectional correlations of MR images with EDSS. Limited number of studies examined EDSS and MRI correlations in patients with Transverse Myelitis. MRI images can help predict recovery progress based on lesion characteristics.

**Methods:** We conducted a retrospective review of the last 42 monophasic TM admissions to the Johns Hopkins Hospital. Inclusion criteria included a single inflammatory attack localizing to the spinal cord presenting with a change in neurological examination and a new MRI lesion. Subjects were excluded if their TM was part of a recurring disease or if they tested positive for the

NMO-IgG blood test. Extended Disability Status Scale (EDSS) score was calculated at baseline, at presentation, at discharge, and on follow-up. MR images were examined and broken down by

1. Number of Vertebral Bodies
2. Lesion Location
3. Length of the lesion (cm or mm?)

Results of the MRI were compared to the EDSS scores to evaluate outcome based on lesions characteristics.

**Results:** Of the 42 subjects enrolled, 37% with Long Lesion (more than 4 vertebral bodies) showed improvement by at least 1 point at one year follow up on EDSS exam. Whereas 19% with Short Lesion (3 or less vertebral bodies) show improvement from admission to one year follow up.

**Conclusions:** Longer lesion on MR images from admission to follow up resulted in better long term recovery outcome.

### Disclosure

Nothing to disclose

### EP1549

#### Resting state functional networks and cognitive performance in clinically isolated syndromes

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**Introduction:** Cognitive impairment in multiple sclerosis (MS) has been related to structural brain damage, but the mechanisms linking these two phenomena are unclear. Resting-state functional MRI (rsfMRI) is a promising method to evaluate this link, since abnormal functional connectivity (FC) patterns may reflect either maladaptive or compensatory mechanisms, favouring or limiting clinical consequences of structural brain damage even from early stages of MS. Independent component analysis (ICA) is a tool to study FC by decomposing within-voxel BOLD signal into different components. Voxel clusters with temporally correlated components form the specific resting-state functional networks (RSN), with clearly defined cognitive roles.

**Aims:** To characterise, in patients with a clinically isolated syndrome (CIS), the different RSN and the association between FC within the RSN and cognitive performance.

**Methods:** We included 19 CIS patients (9 female, mean age 36±9 years) and 12 healthy controls (HC, 8 female, 35±8 years). All subjects were scanned (T1- and T2-weighted images, rsfMRI) in a 3T scanner. Patients underwent cognitive assessment (Symbol Digit Modalities Test, SDMT). CONN-FC toolbox was used to extract RSN with ICA and to perform statistical analyses: generalised linear models adjusted for age and gender. P-value thresholds to define significance were < 0.001

(uncorrected) at the voxel level and < 0.05 (FDR-corrected) at the cluster level.

**Results:** None of the RSN showed significant differences in within-network FC between groups. Yet using a more liberal threshold ( $p < 0.05$  at voxel level), patients showed a trend towards higher FC in the default mode ( $b = 0.82$ ,  $p < 0.0001$ ) and frontoparietal ( $b = 0.54$ ,  $p < 0.01$ ) RSN, and lower FC in the dorsal-attention network ( $b = -0.73$ ,  $p < 0.01$ ) than controls. In patients, lower FC in several RSN (including frontoparietal and dorsal-attention RSN) was associated with worse cognitive performance ( $b = 0.04$ ,  $p = 0.004$ ). Instead, higher FC in the salience RSN (precuneus) was associated with lower cognitive performance ( $b = -0.06$ ;  $p = 0.006$ ).

**Conclusions:** In early CIS, FC within RSN is relatively intact. However, a trend towards altered FC in areas strongly associated with cognition was observed in patients. Longitudinal studies will address whether these findings indicate an incipient FC deterioration in the CIS, therefore reflecting both maladaptive and compensatory mechanisms leading to or limiting cognitive decline in MS.

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### EP1550

#### Information processing and brain flexibility in multiple sclerosis: the relevance of state-contrast

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**Background:** Information processing (IP) problems are prevalent in MS, and might be related to changes in dynamic functional connectivity (*flexibility*) of the default mode network (DMN) and fronto-parietal network (FPN). We explored DMN and FPN flexibility during IP, during rest and in relation to each other with respect to IP. Additionally, we explored differences between patients switching to fingolimod treatment (FT) and patients on standard (first-line) treatment (ST), in order to investigate whether the decision to change medication might be reflected by changes in flexibility.

**Methods:** Thirty-two MS patients (14 FT and 18 ST patients), and 18 healthy controls (HCs) were included. The Letter Digit Substitution Test (LDST) was used to assess IP performance. Lesion load, gray matter volume (GMV) and white matter volume were measured using magnetic resonance imaging (MRI; 3T). Functional MRI was obtained during an IP-task (Symbol Digit Modalities Test) and during rest. Using a sliding window approach DMN and FPN flexibility in both states were calculated, and the flexibility ratio between states for each network (IP-task/resting-state (RS) flexibility) was explored using Pearson correlation coefficient. LDST performance was predicted using forward linear regression analysis.

**Results:** No differences in age, sex, and educational level were found between MS patients and HCs. Compared to HCs, MS patients performed worse on the LDST and had lower GMV ( $P < 0.01$ ). No differences in flexibility were found. The relationship between IP-task and RS flexibility of the DMN was positive ( $r=0.40$ ,  $P=0.10$ ) in HCs, but negative in MS ( $r=-0.44$ ,  $P=0.01$ ) and driven by FT patients (no difference was found for the FPN). Better LDST performance in MS could be predicted by a larger IP-task/RS flexibility ratio of the DMN ( $\beta=0.53$ ,  $P < 0.001$ ) and larger GMV ( $\beta=0.39$ ,  $P < 0.01$ ). FT and ST patients did not differ on demographic or MRI measures. In FT patients, 77% of variance in IP performance could be explained by the IP-task/RS flexibility ratio of the DMN ( $\beta=0.76$ ,  $P < 0.001$ ) and GMV ( $\beta=0.37$ ,  $P=0.02$ ), whereas in ST patients, 27% of IP performance could be explained by lesion load ( $\beta=-0.56$ ,  $P=0.02$ ).

**Conclusion:** Next to GMV, greater IP-task/RS flexibility contrast of the DMN is important for IP in MS. This might suggest that if the DMN is better able to switch flexibility between states, it will benefit IP. Future studies should explore if this contrast is an indication for switching therapy.

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## EP1551

### Longitudinal variation in structural and diffusion parameters of fatigue patients in multiple sclerosis

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Sood, C. Santiago, N. Seraji-Bozorgzad, E. Bernitsas

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**Objective:** To investigate the relation between volumes of sub-cortical structures, diffusion properties of cortical lobes and fatigue score variation between two time points in Multiple Sclerosis.

**Background:** Fatigue affects 80-90% of Relapsing Remitting Multiple Sclerosis patients (RRMS). However, consistent longitudinal imaging correlates to changes in severity of fatigue remain elusive. Prior studies have implicated the role of thalamus, frontal and parietal lobes, corpus callosum and various white matter tracts in pathogenesis of fatigue in RRMS patients. The thalamic volume variation was reported to be significant in longitudinal studies on fatigue in MS.

**Methods:** 46 RRMS patients who reported MS-related fatigue (Fatigue Severity Scale (FSS) mean score: 1 - 7) were involved in this longitudinal retrospective imaging study at baseline and year one. Other causes of fatigue were excluded. Patients were relapse-free and not on steroid treatment within the last 3 months prior to screening. All patients had T2, MPAGE and DTI images using the same MRI protocol. Using FreeSurfer program, we calculated the deep gray matter volumes and cortical thickness. Cross-modality technique was used to measure the DTI parameters of cortices. Pearson correlation was used to test the relationship between the variables.

**Results:** The pallidal volume ( $r^2=0.292$ ,  $p < 0.04$ ) and right temporal cortex radial diffusivity ( $r^2=0.314$ ,  $p < 0.02$ ) variation between two time points had significant inverse correlation with baseline fatigue score.

**Conclusion:** The changes in pallidal volume and radial diffusivity of right temporal cortex between the two time points reflects prognosis of fatigue in RRMS. Future research will focus on the association between volumetric changes of specific structures in RRMS population and fatigue score at the above time points, using tract based spatial statistics of structural and diffusion data.

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#### EP1552

##### **Magnetic resonance fingerprinting indicates thalamic atrophy in multiple sclerosis and reflects extrinsic pathology**

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**Introduction:** Thalamic atrophy, a prominent feature in multiple sclerosis (MS), may occur as a consequence of intrinsic thalamic pathology and/or due to distant injury in white matter tracts. Magnetic resonance fingerprinting (MRF) is a new MRI approach that provides direct estimates of quantitative relaxation times from fast acquisition.

**Objectives:** To investigate quantitative MR properties using MRF in the thalamus of MS patients compared with controls, and to correlate extrathalamic involvement with quantitative changes in thalamic tissue.

**Methods:** Nine patients with relapsing remitting (RR) MS (disease duration [DD]  $\leq 5$  years, EDSS  $\leq 2$ ), 9 patients with secondary progressive (SP) MS (DD  $\geq 10$  years, EDSS  $\geq 4.0$ ), and 8 age/gender matched controls were recruited. Clinical measures included EDSS, MSFC, and neurocognitive testing. MRI of the brain was conducted with FISP-MRF protocol (1000 images, 1.2 x 1.2mm, 20 slices, 5mm slice thickness) and conventional MRI (T1-weighted MPRAGE, 3D FLAIR, and 3D T2). Thalamic were segmented using an atlas-based approach. Lesions (T1/T2) and white matter structures were segmented. Mean T1 and T2 relaxation times were measured within each region of interest (thalamus, frontal normal appearing white matter, corpus callosum, caudate, T1 lesions, and T2 lesions). Differences between controls, RRMS, and SPMS were analyzed by ANCOVA with age as covariate. Correlations were assessed between MRI and clinical measures using Pearson test.

**Results:** Thalamic volumes were significantly different between controls (20.5 ml, SD: 0.7), RRMS (20.2 ml, SD: 1.4), and SPMS patients (16.6 ml (1.7ml) ( $p < 0.001$ ). Thalamic T1 and T2 relaxation did not show consistent differences in controls, RRMS and SPMS. There was no correlation between thalamic volume and T1 and T2 relaxation times from the thalamus. In contrast, significant correlations were found between thalamic volume and T1 relaxation times from white matter T2 lesions ( $r = -0.74$ ,  $p < 0.001$ ) and T1 lesions ( $r = -0.61$ ,  $p = 0.01$ ). Significant correlations were found between thalamic volume and SDMT ( $r = 0.78$ ,  $p < 0.001$ ) and EDSS ( $r = -0.67$ ,  $p < 0.002$ ).

**Conclusions:** Thalamic volume distinguishes MS from controls, RR from SPMS, and correlates with both physical and cognitive measures of impairment. Thalamic atrophy reflects extrathalamic injury measured in T1 and T2 lesions with no clear relationship between thalamic volume and intra-thalamic T2 and T1 relaxation times.

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#### EP1553

##### **Intracranial volume as a surrogate for maximal lifetime brain growth in adult-onset multiple sclerosis: comparison with healthy controls**

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**Introduction:** Overall intracranial volume (ICV), which in part reflects maximal lifetime brain growth (MLBG), has been reported to be decreased in pediatric multiple sclerosis (MS) patients in comparison to age- and sex-matched healthy controls (HCs), suggesting that the pediatric-onset MS may affect primary brain and skull development. In adults, MS clinical symptom-onset typically occurs between the ages of 20-30; however, the majority of patients already have evidence of brain atrophy on MRI at diagnosis, suggesting that biological disease onset started at an earlier timepoint. We previously demonstrated that head circumference (as a surrogate of ICV) was decreased in adult-onset MS patients vs. HCs. To our knowledge, ICV, as an assessment of MLBG, has not been compared between adult-onset MS patients and HCs.

**Objective:** To compare ICV (as an assessment of MLBG) in MS patients with disease onset in adulthood vs. HCs.

**Methods:** MRI measures, including ICV and brain parenchymal fraction (BPF), were assessed in 106 MS patients and 112 HCs balanced for age and sex using Voxel-based Morphometry 8 (VBM8) toolbox for SPM8. Student's t-tests compared ICV in

MS vs. HCs. Multivariable linear regression was performed to compare ICV in MS vs. HCs while controlling for potentially confounding covariates of age and sex.

**Results:** MS patients were a mean age of 43 years, 69% female, and had a mean age at clinical diagnosis of 32 years. HCs were a mean age of 45 years, and 63% female. Mean ICV was lower in MS ( $1395.66 \pm 14.67 \text{ mm}^3$ ) vs. HCs ( $1426.52 \pm 14.98 \text{ mm}^3$ ); but this result did not reach statistical significance ( $p=0.14$ ). In MS patients with earlier clinical disease onset ( $\leq 40$  years;  $n=79$ ), mean ICV ( $1387.33 \pm 16.73 \text{ mm}^3$ ) was even lower, with a trend towards significance ( $p=0.08$ ), particularly when controlling for potentially confounding variates of age and sex ( $p=0.05$ ). As expected, there was also clear evidence of brain atrophy in MS vs. HCs as measured by BPF ( $0.816 \pm 0.002$  vs.  $0.834 \pm 0.001$ ;  $p < 0.001$ ).

**Conclusion:** MS patients with clinical disease-onset in adulthood show trends towards having smaller ICVs in comparison to HCs, particularly when clinical symptom onset is before the age of 40. If confirmed in larger cohorts, these findings suggest that even when MS clinically manifests in adulthood, pathologic processes affecting MLBG may begin during periods of brain and skull growth in childhood or early adolescence, which is substantially earlier than expected.

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## EP1554

### Verbal memory and brain micro-structural changes in multiple sclerosis

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**Background:** Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system involving both white and

grey matter. Brain diffusion tensor imaging (DTI) enables in vivo, detection of pathological micro-structural changes that are not recognized in conventional MRI scans.

**Aim:** To identify brain areas with altered micro-structure that correlate with verbal memory impairment in relapsing remitting MS patients (RRMS).

**Methods:** A retrospective cross sectional study was conducted in 63 RRMS patients who completed:

- 1) Mindstream computerized cognitive evaluation tests (MCCT);
- 2) EDSS evaluation;
- 3) an MRI scan including diffusion tensor imaging (DTI).

All data were obtained within three months. Quantitative parameters as fractional anisotropy (FA) were derived from the DTI scans using in house developed Matlab software. Image processing and statistical analysis were based on voxel based analysis (VBA) using Statistical parametric mapping (SPM 8) and brain visualization performed with the xjView toolbox.

**Results:** 63 RRMS patients were included in the study {F/M 45/18; age 31 years (21-46); disease duration  $5.2 \pm 3.1$  years; EDSS  $2.0 \pm 1.7$ }. Six statistically significant clusters were identified (family wise error corrected for multiple comparisons,  $p < 0.005$ ), in which FA correlated with verbal memory MCCT scores ( $96.8 \pm 16.2$ ). The clusters included: right hippocampus, right and left para-hippocampus, right and left cerebellum, right and left thalamus, right fusiform gyrus and right insula (xjView toolbox).

**Conclusions:** Lower FA values and micro-structural changes in specific brain areas were significantly correlated with a decline in verbal memory scores on MCCT. We describe specific changes in brain microstructure which cannot be seen in anatomical brain MRI. The VBA-DTI methodology could be used in cognitively affected MS patients, to identify changes in brain regions related to cognitive tasks.

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## EP1555

### OFSEP MRI protocol: the need of good practice's standardization from clinicians to scientists

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EDMUS contre la Sclérose en Plaques, Hôpital Neurologique

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OFSEP (Observatoire Français de la Sclérose en Plaques) is a national cohort of patients with MS and related disorders, set up in 2010 from a rich historical background use of EDMUS in France. It aims at collecting standardized, high-quality, longitudinal data, including clinical, biological and imaging follow-up of patients with MS and makes it available to the research and industrial community and health authorities. In December 2016, more than 54.000 clinical files were available, progressively enriched with biological and imaging data. Over the past two decades, the clinical use of MRI in patients with MS has considerably impacted the diagnostic procedure as well as prognostic indicators, including evaluation of the treatment-response up to the concept of "No Evidence of Disease Activity". Therefore, standardized MRI examinations only can allow a reliable comparison of successive MRIs over time that will guide therapeutic decision. The OFSEP imaging group designed a consensus standardized MRI protocol that could fulfil the needs of clinician in their decision-making process but also be available for research purpose. The group worked closely with main MRI companies to promote the MRI "OFSEP protocol" in an "exam card" available on all new system (see ofesp.org). MRI data are transferred and stored onto a centralized national facility, Shanoir, with respect to privacy protection in agreement with French national authority (CNIL). All the data are pseudonymized locally on the hospital computer prior to the transfer; this step allows inter-operability with biological and clinical databases for research. We are currently in the process of spreading the MRI protocol across French MRI centres. 18 centres started to export MRI data mainly through PACS connection to load their data retrospectively. All the data collected will be then available to the research community as well as the biological and clinical databases.

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## EP1556

**[<sup>18</sup>F]-Florbetaben-PET/MRI as myelin-specific molecular imaging: a pilot study in patients with different white matter diseases**

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**Background:** PET imaging with tracers such as [<sup>18</sup>F]Florbetaben (FBB) allows the in vivo visualization of cortical  $\beta$  amyloid (A $\beta$ ) depositions as occurring in Alzheimer's disease. FBB also - independently from A $\beta$  - binds to brain white matter (WM) myelin, suggesting a potential value in imaging multiple sclerosis (MS). After promising preliminary results, further studies employing this tracer in other WM diseases are currently missing.

**Objectives:** To assess in vivo quantification of FBB uptake in patients with different WM diseases in comparison to non-WM diseased controls. We hypothesized a decreased WM tracer accumulation in the patient group as a surrogate of myelin loss.

**Methods:** We examined 13 patients with pathophysiologically distinguishable WM diseases (MS [n=4]; progressive multifocal leukoencephalopathy [PML, n=3]; adult-onset leukodystrophy [genetically determined, n=3]; cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL, n=3]) and concurrent mild cognitive impairment using FBB-PET/MRI. 13 age- and gender-matched patients with cognitive impairment but without WM disease served as controls. PET data were acquired 90-110min after injection of FBB using a simultaneous PET/MR System (Biograph mMR, Siemens). Segmentation of WM and generation of standard volumes of interests (Automated Anatomical Labeling atlas) was performed in PMOD 3.5. WM lesions were segmented by the lesion prediction algorithm as implemented in the LST toolbox for SPM. We determined the WM standardized uptake value (SUV) ratio (SUV<sub>WM</sub>) using the cerebellar cortex as reference region. For WM diseases, the WM lesion SUV Ratio (SUV<sub>WM</sub>) was calculated using the same reference.

**Results:** SUV<sub>WM</sub> were significantly lower in patients than controls (1.78 $\pm$ 0.32 vs. 1.90 $\pm$ 0.14, p=0.04). Within the patient group, WM lesions showed an even lower tracer retention than normally appearing WM (SUV<sub>WM</sub> vs. SUV<sub>WM</sub>: 0.98 $\pm$ 0.22 vs. 1.78 $\pm$ 0.32, p<0.001). These findings were independent of the cortical tracer uptake. An additional subgroup analysis regarding WM uptake degree and distribution between the different WM diseases is planned after recruitment of a larger cohort.

**Conclusion:** Patients with pathophysiologically different WM diseases show decreased FBB WM binding, especially in WM lesions, compared to non-WM-diseased controls. Further research in larger cohorts is justified to investigate the potential of FBB PET/MRI in evaluating demyelinating diseases.

## Disclosure

SH has no conflicts of interest with respect to the contents of this abstract. Within the past year before abstract submission, she has received support to attend a scientific meeting from Merck-Serono and Actelion.

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HB received research support, consultant honoraria, and travel expenses from Piramal Imaging related to this abstract. Within the past year before abstract submission, he received consulting honoraria and travel expenses also from Siemens Healthcare.

#### EP1557

##### **Basal ganglia volume and cognitive function in newly diagnosed and untreated multiple sclerosis patients**

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**Background:** Cognitive impairment is frequent, debilitating and can be present early in the disease course of multiple sclerosis (MS). The basal ganglia are deep grey matter structures involved in cognitive tasks, and frequently affected in MS patients. Abnormal basal ganglia activation on functional MRI has been observed during cognitive testing and lower volume has been associated with cognitive dysfunction. However, these studies were mainly conducted in treated patients and associations may differ in newly diagnosed treatment-naïve patients.

**Objectives:** To assess the relationship between basal ganglia volume and cognitive function in untreated MS patients.

**Methods:** In total 68 untreated relapsing-remitting MS patients with short disease duration underwent brain MRI in the context of a previously reported randomized clinical trial (OFAMS). Their mean age was 38 years, mean time from diagnosis 1.7 years and mean EDSS 1.9±0.8. MRI scans were pre-processed using FreeSurfer-software estimating automatically total and constituent basal ganglia volume, including caudate nucleus, putamen, pallidus, and nucleus accumbens. Manual verification/editing followed. Cognitive function was assessed within ± 7 days of the MRI examination by Paced Auditory Serial Addition Test (PASAT), a validated tool, especially sensitive to MS-related processing speed and attention deficits. We estimated Pearson's correlation coefficients between basal ganglia and specific nuclei volumes and PASAT.

**Results:** We observed a statistically significant relationship of moderate strength between the basal ganglia volume and PASAT score. The correlation coefficient was strongest for total volume ( $r=0.28$ ;  $p=0.027$ ), but of similar magnitude for the single nuclei: putamen ( $r=0.26$ ,  $p=0.043$ ), caudate nucleus ( $r=0.25$ ;  $p=0.040$ ), pallidus ( $r=0.22$ ;  $p=0.089$ ), and nucleus accumbens ( $r=0.25$ ;  $p=0.048$ ).

**Conclusions:** In this untreated MS patient population with short disease duration and low physical disability, we observed that basal ganglia volume was significantly associated with cognitive function as measured by PASAT. Basal ganglia volume may be an

early indicator of cognitive impairment and its use could be considered in prognostic scores at the first MRI in a clinical setting.

**References:** Torkildsen O, Wergeland S, Bakke S, et al. *ω-3 fatty acid treatment in multiple sclerosis (OFAMS Study): a randomized, double-blind, placebo-controlled trial*. Arch Neurol 2012;69:1044-51.

#### **Disclosure**

M. Cortese reports no disclosures.

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#### EP1558

##### **Clinicoradiological correlation revisited in relapsing onset North African multiple sclerosis**

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Multiple sclerosis (MS) shows variable disease characteristics at different ethnicities and geographical regions. Magnetic resonance imaging (MRI) features of MS are not adequately described in African Mediterranean region. We aimed to describe main clinical and MRI features of MS in Egyptian patients.

Relapsing onset MS patients ( $n=47$ ) and a group of age and sex matched healthy controls ( $n=20$ ) were recruited. All subjects had a standardized clinical evaluation, and an MRI examination (1.5 Tesla scanner, FLAIR and T2 for lesion load (LL) estimation and a sagittal 3D-T1 for volumetric assessment). Analysis included LL estimation (MIPAV software), whole brain atrophy (SIENAX method), subcortical segmentation (FIRST part of FSL software) and mean upper cord cross-sectional area CSA. Correlation between clinical and MRI parameters were done using partial correlation.

Mean disease duration was 5.8 (4.96) years (SD), only 10 patients were under any of the disease modifying treatments. Normalized Whole brain volume (NWBV) was significantly lower in MS group compared to controls ( $p=0.008$ ), and the thalamic fraction (volume of both thalami divided by total intracranial volume) ( $p=0.001$ ), right and left hippocampi ( $P=0.006$  and  $0.06$  respectively), but not with the normalized grey matter volume or the cord cross-sectional area (CSA).

EDSS correlated well with lesion load ( $p=0.005$ ,  $r=0.44$ ), NAWV ( $p=0.01$ ,  $r=0.48$ ), normalized cortical volume ( $p=0.001$ ,  $r=0.58$ ), thalamic fraction ( $p=0.03$ ,  $r=0.36$ ), caudate fraction ( $p=0.001$ ,  $r=0.43$ ) and cord CSA ( $p=0.03$ ,  $r=0.43$ ).

MRI features of MS in North African population appear to be replicating what has been known from other MS studies elsewhere. However smaller intracranial volume and cord CSA even in healthy controls compared to available data from western and European countries. We postulate that these smaller values represent a smaller tissue reserve that might interpret the relatively better correlation between lesion load and clinically disability compared to other studies, and might also explain the relatively more aggressive nature of the disease in Africa.

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 Prof. Hussien Mohammad has nothing to disclose  
 Dr Abdalla Metwally has nothing to disclose  
 Dr Mohammad Aboulwafa has nothing to disclose  
 Dr Mohammad Atallah has nothing to disclose

### EP1559

#### New and enlarging lesion location for different MS clinical phenotypes

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**Purpose:** Evaluate the location of lesion evolution for different MS clinical phenotypes using MSmetrix.

**Materials and methods:** Longitudinal MRI follow-up of 12 clinically isolated syndrome (CIS), 30 relapsing remitting (RR), 17 primary progressive (PP) and 28 secondary progressive (SP) MS patients was conducted using a 1.5 Tesla MR system (Sonata Siemens). For each patient, two time points at least 2 years apart were selected in order to estimate medium-term lesion evolution. MSmetrix employs T1-weighted and FLAIR images at two time points to estimate brain tissue and lesion segmentations and volumetry, as well as volume changes in time. Moreover, the lesions are classified according to brain location. Volumes of new or enlarging lesions classified by MSmetrix as juxtacortical lesions, periventricular lesions or deep white matter lesions, were compared between the four patient groups (CIS, RR, PP and SP).

**Results:** CIS patients showed the largest volume of new lesions (i.e., lesions not touching any older lesion), with an average volume of only 0.1 ml in each of the three locations (juxtacortical, periventricular, deep white matter). PP and SP patients had on average lower new lesion volumes ( $< 0.06$  ml), with almost no new lesions in the periventricular region. This was compensated by large volumes for lesion enlargement, especially in the periventricular region. Although all groups show lesion enlargement mostly in the periventricular regions compared to other regions, some significant differences between groups were observed: PP patients showed the most enlargement in the periventricular region (median 3.8 ml), significantly higher than for CIS and RR, but comparable to the SP group. The RR group showed more

enlargement of deep white matter lesions compared to the other groups, with a median of 0.1 ml. There were no significant differences between clinical groups in the volumes of enlarged juxtacortical lesions (median value 0.05 ml for all groups).

**Conclusion:** MSmetrix found a location-dependent evolution of new and enlarging lesions for different MS clinical phenotypes. Some of the findings can be explained by disease duration: more advanced MS forms (PP and SP patients) show significant enlargement of existing periventricular lesions instead of new lesion formation. Compared to other groups, RR patients had more enlargement of the deep white matter lesions, and for CIS patients there seemed to be no location prevalence in the appearance of new lesions.

### Disclosure

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 Dominique Sappey-Marini: nothing to disclose.  
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### EP1560

#### Can MR permeability and contrast enhanced (CE)-FLAIR demonstrate AQP4 channel dysfunction in NMOSD patients? Work in progress

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**Objective:** NMO spectrum disorders [NMOSD] are putatively accepted as inflammatory autoimmune diseases of the CNS. Imaging findings in NMOSD are distinct from MS. We previously observed leptomeningeal (LM) contrast enhancement in 4 of our 46 NMOSD patients during their attack. Recently imaging findings consistent with LM blood-CSF barrier disruption and transient leakage of contrast agent into the subarachnoid space was shown in NMOSD patients during attack. AQP4 is highly expressed throughout the CNS including grey matter. Aquaporin channels are considered to have essential functions in glymphatic system. The anatomical integrity of this pathway has been supported by astrocytic end-foot with AQP 4 water channels. These findings suggest that AQP channel pathology might be more spread than restricted to typical parenchymal areas. Our aim is to evaluate further AQP4 channel dysfunction leading to LM blood-CSF barrier disruption by studying dynamic contrast-enhanced (DCE) MR perfusion and contrast enhanced (CE)-FLAIR in clinically stable NMOSD patients.

**Material and method:** 19 patients were diagnosed as NMOSD according to the new diagnostic criteria. All patients were in remission under treatment. We evaluated dynamic contrast-enhanced (DCE) MR perfusion and contrast enhanced (CE)-FLAIR in addition to routine brain MRI from 19 NMOSD patients with no disease activity.



**Results:** Median age of our patients was 44.1 years old. 15 of them were female, 4 of them were male. 12 of patients were positive for AQP4 antibody, 3 were positive for MOG antibody, one of them was positive for both. 3 of them were seronegative. Mean disease duration was 6.9 years. 5 of our patients had other autoimmune diseases. All of our patients were under immunosuppressive/modulatory treatment. We identified 2 patients with NMOSD who have LM contrast enhancement in post-contrast (PC) FLAIR series while PC T1W images were normal and had no evidence of disease activity. First patient was 41 years old female. She displayed both aquaporin and MOG antibodies. CE-FLAIR revealed abnormal LM and sulcal enhancement. Second patient was 53 years old female. She was seronegative for both antibodies. She also had Sjögren's. CE-FLAIR revealed abnormal LM and sulcal enhancement. Our DCE-MR permeability data from our patients is being processed.

**Conclusion:** We propose that AQP4 channels may contribute to the brain microcirculation in glymphatic pathway therefore related sequences of MRI can be used to prove this hypothesis.

## Disclosure

Nothing to disclose

## EP1561

### Racial and environmental influences on North African multiple sclerosis, application of global and regional brain atrophy measures

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Well validated methods has been used to evaluate brain atrophy in multiple sclerosis (MS) patients, however to our knowledge these methods has not been well applied to African multiple sclerosis patients which are expected to have different profile of genetic and environmental factors that influence brain volume.

We aimed to evaluate the SIENAX method application among North African patients with MS. Three groups were recruited; a group of relapsing onset Egyptian MS patients (n=47), a group of Egyptian healthy controls (n=30), and a third group of healthy controls from the publicly available OASIS MRI database (n=181) for comparing the possible influence of racial and environmental factors. The three groups were matched for both age and sex.

We used a 1.5T Philips scanner for acquisition of a 3D T1 volume of the brain, and a FLAIR sequence for lesion load. Analysis included Lesion Load (LL) estimation (MIPAV software), Normalized Brain Volume (NBV) (SIENAX method) after performing adequate lesion masking in the MS patient group, subcortical segmentation (FIRST part of FSL software).

For MS patient group mean disease duration was 5.8 (4.96) years (SD), only 10 patients were under any of the disease modifying treatments. Total intracranial volume was highly significantly lower at the Egyptian Population (1245.07 (SD 115.72)) ml (patients and controls) compared to OASIS database (1480.50 (SD 158.30)) ml ( $p < 0.001$ ). Normalized brain volume was also highly significantly lower between Egyptian healthy controls (76.7% of intracranial volume SD 0.05%) and OASIS database (84.1% of intracranial volume SD 0.02%) ( $p < 0.001$ ).

NBV was significantly lower among MS Patients 1427.35 (SD 97.45) ml compared to Egyptian healthy controls 1494.2 (SD 72.21) ml ( $p=0.008$ ). Thalamic fraction was significantly lower (calculated as the volume of both thalami divided by intracranial volume) in patients compared to controls ( $p=0.001$ ), hippocampi ( $P < 0.002$  and  $P < 0.01$  right and left), but were not different in normalized cortical volumes or cord cross-sectional area.

Racial and environmental factors appears to clearly influence brain volume in health and disease conditions. SIENAX and FIRT methods for evaluation of global as well as regional brain atrophy were able to demonstrate differences between healthy controls and north African MS patients. Careful consideration of generalizing the brain atrophy measurements across different geographical, environmental as well as racial factors.

## Disclosure

Professor Fathi Afifi has nothing to disclose

Dr Mohammad Aboulwafa has nothing to disclose

## OCT

## EP1562

### OCT in familial and sporadic MS patients: correlation between RNFL and macular volume

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**Goal:** The aim of this study was to determined correlation between retinal nerve fiber layer (RNFL) thickness and the macula volume (MV) measured by spectral- domain OCT (SD-OCT) in familial (fMS) and sporadic (sMS) multiple sclerosis patients.

**Background:** . There is unresolved issue whether sMS differs from familial form of disease. Optical coherence tomography (OCT) allows quantification of retinal structures, such as RNFL thickness and MV. RNFL thickness is considered as a marker of axonal loss and MV as a marker of neuronal integrity.

**Patients and method:** 71 RR MS patients (31 fMS, 40 sMS) age and gender matched were included in the study. Familial MS was defined based on whether or not the proband case had a first-degree relatives with MS. Both MS groups were matched according to neurological status measured by EDSS, annual relapse rate in previous 2 years and disease duration. All patients underwent SD-OCT examination (Spectralis, Heidelberg Engineering). Total RNFL thickness and MV were assessed in right and left eyes and were expressed as a mean value for each patients.

**Results:** RNFL thickness in fMS was lower than in sMS but this difference was not significant ( $94.90 \pm 10.8$  vs  $97.2 \pm 8.4$   $p=0.4$ ). Mean MV was lower but not significantly in fMS compared to sMS ( $8.2 \pm 1.0$  vs  $8.4 \pm 0.3$   $p=0.08$ ). There was a correlation between mean RNFL thickness and MV in both forms of MS (fMS  $r=0.4$ ,  $p=0.01$  and sMS  $r=0.5$ ,  $p=0.0001$ ) however the this correlation was stronger in sMS patients.

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Prof. K Selmaj: nothing to disclose

## EP1563

**Evaluation of the neurodegeneration processes in dynamics in multiple sclerosis**

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The retina is a unique part of the CNS that contains glia and axons devoid of myelin in the retinal nerve fiber layer (RNFL), which makes them ideal for evaluation of neurodegeneration and neuroprotection.

The aim: to study the possibilities of the optical coherent tomography (OCT) method in the neurodegeneration processes monitoring in patients with MS.

**Material and methods:** 145 patients (285 eyes) were examined. OCT was carried out with the Cirrus 500 HD. The main group consisted of 114 patients (223 eyes) with MS according to McDonald criteria (2005, 2010). Most of the patients included in the study had relapsing-remitting course, 10.5% - secondary-progressive. For 46 patients (40% of the total), at least 2 OCT studies were obtained at an interval of about 12 months (352±152 days). Exclusion criteria: high degree of myopia, glaucoma, diabetes mellitus, other CNS diseases. The control group is 31 healthy volunteers (62 eyes).

**Results:** The mean macular volume in MS patients ( $9.8 \pm 0.5 \text{ mm}^3$ ), the average thickness of the macula ( $248 \pm 26 \mu\text{m}$ ) were significantly lower in comparison with the control. The average thickness of the RNFL in the main group was  $85.6 \pm 11 \mu\text{m}$  (in the control group -  $96 \pm 8 \mu\text{m}$ ), and RNFL was minimal in the temporal sector ( $56 \pm 12 \mu\text{m}$ ). The highly sensitive and specific marker of neurodegenerative changes in the retina in MS are the temporal segments of RNFL (T, TI, TS). The thickness of the ganglion cells layer (GCL) of the retina was significantly lower in MS ( $72 \pm 9 \mu\text{m}$  versus  $83 \pm 5 \mu\text{m}$ ,  $p < 0.05$ ). Significant negative correlations between the dynamics of thinning of the GCL and an increase in the EDSS during the observation period were observed. The most significant correlations were revealed in the temporal and upper sectors of GCL ( $r = -0.44 \dots r = -0.58$ ,  $p < 0.05$ ). These sectors can be considered promising markers of MS progression. The change in the GCL in dynamics was in the temporal segments mostly: the average thickness decreased by  $0.35 \mu\text{m}$  during observation, and the thickness of the temporal and upper sectors decreased on average by  $0.74 \mu\text{m}$  and  $0.37 \mu\text{m}$ , respectively.

**Conclusions:** The dynamics of thinning of the GCL and RNFL in patients with MS correlates with an increase in neurological deficit and disease progression. Evaluation of OCT in dynamics every 12 months allows to objectify and monitor the neurodegenerative process in MS, which is necessary for predicting the course and selection of adequate therapy.

**Disclosure**

All authors: nothing to disclose.

## EP1564

**Retinal optical coherence tomography in chronic relapsing inflammatory optic neuropathy: a retrospective analysis of distinctive features**

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**Objective:** To assess the distinctive features of retinal structure in chronic relapsing inflammatory optic neuropathy (CRION) as compared to other optic neuropathies in neuromyelitis optica (NMO) and relapsing remitting multiple sclerosis (RRMS).

**Background:** CRION is a recurrent, steroid responsive optic neuritis without any additional neurological deficits. Diagnosis is made clinically, after recurrent attacks and exclusion of other demyelinating pathology. We used optical coherence tomography (OCT) to assess potential retinal features that may distinguish CRION from NMO and RRMS.

**Design/methods:** Spectral domain OCT was used to evaluate and compare the retinal layers of 35 eyes with optic neuritis in patients with CRION (8 eyes), NMO (13 eyes), RRMS (14 eyes) and 10 eyes of healthy controls (HC). The subjects were adjusted for age, disease duration and number of relapses. Peripapillary retinal nerve fiber layer (p RNFL) within superior, inferior, temporal, nasal and total macular volume (TMV) and papillomacular bundle (PMB) were measured and intra-retinal segmentation was performed to obtain retinal nerve fiber (RNFL), ganglion cell (GCL), inner plexiform (IPL), inner nuclear (INL), outer plexiform (OPL) and outer nuclear (ONL) layer thickness.

**Results:** pRNFL thinning was demonstrated in patients with CRION ( $52.46 \pm 8.3 \mu\text{m}$ ) as compared to HC ( $86.8 \pm 7.6 \mu\text{m}$ ,  $P\text{-value} = 0.021$ ) and RRMS ( $75.2 \pm 4.5 \mu\text{m}$ ,  $P\text{-value} = 0.009$ ) but not NMO patients ( $69.15 \pm 5.03 \mu\text{m}$ ,  $P\text{-value} = 0.13$ ). Within quadrants analysis, inferior quadrant was statistically thinner in CRION ( $69.31 \pm 11.3 \mu\text{m}$ ) when compared to RRMS patients ( $101.8 \pm 4.8$ ,  $P\text{-value} = 0.007$ ). GCL thickness in macula was significantly thinner in CRION patients ( $0.69 \pm 0.07 \mu\text{m}$ ) when compared to HC ( $0.86 \pm 0.07 \mu\text{m}$ ,  $P\text{-value} = 0.043$ ).

**Conclusion:** pRNFL thickness globally and within inferior quadrant may be used as surrogates to distinguish CRION from other optic neuropathies in particular RRMS. Further longitudinal studies are warranted to confirm these findings.

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**Neurophysiology**

## EP1565

**Neurophysiological correlates of anxiety and depression symptoms in patients with multiple sclerosis: a transcranial magnetic stimulation study**

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**Objectives:** Anxiety and depressive complaints are frequently encountered in patients with multiple sclerosis (MS). Despite their prevalence, no single neurophysiological study has addressed this issue. The main purpose of this work was to assess the relationship between anxiety and depressive symptoms on one side, and cortical excitability measures on the other side.

**Methods:** 50 consecutive MS patients were included in the study. Anxiety and depressive symptoms were scored by the means of Hospital Anxiety and Depression Score. Cortical excitability measures consisted of the following: resting motor threshold, motor evoked potentials amplitudes and latencies, contralateral silent period, short-interval intracortical inhibition, intracortical facilitation and interhemispheric inhibition as previously described [1]. Clinical and socio-demographic data were collected. Correlation analysis was performed to assess the relationship between anxiety or depression and each of the cortical excitability measures.

**Results:** The cohort consisted of 26 men and 24 women. Their mean age was  $51.82 \pm 12.72$  years. Their mean physical disability score was  $5.52 \pm 1.64$ ; their mean disease duration was  $11.88 \pm 6.03$  years. Their mean anxiety score was  $5.82 \pm 3.42$  (range: 1-15); their mean depression score was  $6.08 \pm 3.66$  (range: 0-14). Regarding anxiety scores, they were directly correlated with the mean ( $r=0.43$ ,  $p=0.003$ ) and the maximal values ( $r=0.35$ ,  $p=0.017$ ) of interhemispheric inhibition. As for depression scores, no correlation was found with any of the neurophysiological measures. No other significant correlations were observed.

**Conclusion:** These results are in line with previous studies done in other populations and highlight the relationship between anxiety and callosal transfer [2]. In other words, it seems that MS patients with relatively more efficient callosal transfer tend to have higher stress level and thus higher anxiety scores than those with less efficient callosal function.

**Keywords:** transcranial magnetic stimulation; anxiety; depression; interhemispheric inhibition; hospital anxiety and depression scale.

## References:

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- [2] Leavengood A, Weekes NY. The association between stress, hemispheric specialization, and callosal interactions. *Brain Cogn*. 2000; 43:306-10.

## Disclosure

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## EP1566

### Cortical excitability and alexithymia in multiple sclerosis: a transcranial magnetic stimulation study

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**Objectives:** Alexithymia is frequently encountered in patients with multiple sclerosis (MS). It is a multicomponent personality construct featuring difficulty in identifying feelings or describing them, and an externally oriented thinking. Recent evidence proposes defective GABAergic transmission and deficits in inter-hemispheric transfer behind its occurrence. Such mechanisms could be explored using transcranial magnetic stimulation (TMS). To the best of our knowledge, no single TMS study has been performed in the context of alexithymia in MS patients.

**Methods:** 10 alexithymic and 12 non-alexithymic patients with progressive MS were enrolled based on the 20-item Toronto Alexithymia Scale score (TAS). TMS was used to record the cortical silent period (CSP) and interhemispheric inhibition at different inter-stimulus intervals. Clinical (i.e. Expanded Disability Status Scale, disease duration, progressive phase duration), socio-demographic (age, gender, education level, marital status), and neuropsychological data (i.e. Fatigue Severity Scale, Symbol Digit Modalities Test, Hospital Anxiety and Depression Scale, Epworth Sleepiness Scale) were collected. Group comparison was done using the Mann-Whitney and Fisher's exact tests. In addition, Spearman rank correlation coefficient was used to assess the relationship between TAS scores and each of the cortical excitability measures.

**Results:** Compared to non-alexithymic patients, alexithymic ones had significantly shorter CSP duration (mean:  $159.33 \pm 76.96$ , median: 148.50, vs. mean:  $84.34 \pm 49.73$ , median: 91.50, respectively;  $p=0.03$ ), but did not differ with regards to the remaining excitability data, or clinical, socio-demographic and neuropsychological variables. In addition, a significant inverse correlation was found between TAS scores and CSP ( $r=-0.59$ ;  $p=0.004$ ).

**Conclusion:** This study offers for the first time insights into the neurophysiological mechanisms of alexithymia in MS. Defective GABAergic transmission, particularly that mediated by GABA receptors type B, seems to be associated with alexithymia. Although interesting, these findings warrant further screening in large-scale studies.

**Keywords:** Multiple sclerosis, alexithymia, Toronto alexithymia scale, cortical silent period, cortical excitability, transcranial magnetic stimulation.

## Disclosure

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**EP1567****Cerebral vascular reactivity in multiple sclerosis**

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**Background:** Some studies have suggested that impaired vascular endothelial cell activation might be an early event in multiple sclerosis (MS). Hypercapnia caused by breath holding (BH) results in autoregulatory vasodilatation and an increase in CBF to the cortex. The changes of the CBF can be indirectly assessed by transcranial Doppler (TCD). In this study, we aimed to test the cerebral vascular reactivity of MS patients in response to BH using TCD.

**Methods:** We studied 30 patients with clinically diagnosed relapsing-remitting (RR) MS. The first TCD examination was performed in the relapse (acute exacerbation) phase of the disease and the second test was carried out at least one month later when the patient was in the remission phase. Blood flow velocities were recorded during 30 seconds of normal breathing and subsequently 15 seconds BH. Vascular reactivity was calculated as a ratio of the difference of cerebral flow velocities during BH. Normalisation of the blood flow velocities (decrease to the basal levels after breath holding) and blood flow velocity changes per second were also calculated. Since there was no significant difference between blood velocity parameters recorded on the left and right-hand side, the data were pooled. Thus, 30 patients with 60 vessels were analysed.

**Results:** There were non-significant values between vascular reactivity during relapse (40.5% vs. 36.9%,  $p=0.3$ ) and remission periods. The time to peak velocity (12.5 sec vs. 13.4 sec,  $p=0.3$ ) and the normalisation time (13.8 sec vs. 12.4 sec,  $p=0.15$ ) was quite similar. Also, velocity changes per second were not different between relapse and remission periods (3.4 cm/s vs. 3.0 cm/s,  $p=0.15$ ) for the velocity rise and (5.0 cm/s vs. 4.9 cm/s,  $p=0.8$ ) for velocity decline.

**Conclusion:** This observation suggests that cerebrovascular reactivity is normal in patients with MS during relapse or remission period.

**Disclosure**

Gulnur Tekgol Uzunur: nothing to disclose

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**EP1568****Electrophysiological study of cognitive function through working memory in patients with multiple sclerosis**

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Multiple sclerosis (MS) is a neurological disorder characterized by progressive and extensive lesions in the brain and spinal cord, contemplating motor, cognitive and neuropsychiatric symptoms. Cognitive symptoms comprise between 40 and 70% of MS patients, affecting their functionality in both early and late stages of the disease. Memory impairment is one of the most common cognitive deficits in these patients. This cognitive ability is essential to guide behavior toward achieving goals. As part of short-term memory; Working Memory (WM) plays an important role in the cognitive process of multiple cognitive functions. The

evidence about MS is scarce and contradictory regarding the nature of its cognitive impairment and its evolution.

The aim of the present research is to study the WM using the modification of the Steinberg Paradigm and electrophysiological recording during the requested tasks. Two groups were measured; one of MS patients without the manifest of cognitive alteration and another controlled group of well-matching healthy people. Participants watched arrays of 2, 4 or 6 consonants that had to be memorized. Then a black screen was shown and finally an objective stimulus was displayed (a consonant). The subjects had to respond quickly whether the consonant in the objective stimulus was either present on the array initially shown. We found significant differences in the reaction timing and correct responses in relation to the load of working memory for both the control group and the MS group. However, no significant differences between both groups were found. Regarding to Event-Related Potentials (ERPs), we found modulation in amplitudes of late potentials by memory load in both groups; showing significantly higher amplitudes on the control group. In time-frequency analyses, the both groups showed a reduction in the alpha activity in the end of codification and the beginning of the maintenance. This alpha activity modulation was significantly higher for control group. Furthermore, MS patients showed increased alpha and beta activity in the maintenance stage while, in the recovery stage, patients demonstrated an increase in alpha activity for higher load conditions. Differences in late potentials and in cortical oscillations alpha y beta, electrophysiological variables would be useful in early detecting of alterations in the WM in patients with MS.

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Francisco Aboitiz D: nothing to reveal

Pablo Billeke B: nothing to reveal

**EP1569****Correlation between visual evoked potentials and cognitive impairment in multiple sclerosis patients**T. Erol Yilmaz<sup>1</sup>, N. Bilge<sup>1</sup>, E. Özyildirim<sup>2</sup><sup>1</sup>Neurology, <sup>2</sup>Public Health, *Erzurum Atatürk University, Erzurum, Turkey*

Multiple Sclerosis (MS) affects young adults within a heterogeneous clinical spectrum and it is one of the significant causes of disability in young adults. Cognitive impairment obstructs daily activities of MS patients as much as physical disability causes. This study aims to find out correlation between visual evoked potentials (VEP) and cognitive impairment in MS patients. In this study, cognitive impairment and visual evoked potentials (VEP) are evaluated in 35 RRMS patients who have been followed in neurology outpatient clinic at Ataturk University, Faculty of Medicine and 30 healthy control cases. Wide range of neuropsychometric test battery is applied to patient and control groups including Faces-Symbol Test (FST), Rey Auditory Verbal Learning Test (RAVLT), Digit Span Test (DST), Paced Auditory

Serial Addition Test(PASAT), Face Symbol Test (FST), Clock Drawing Test, Trail Making Test (TMT) and Stroop Test. It was identified that there is impairment in verbal memory processes, attention, retain of attention, working memory, visuospatial functions, executive functions and construction ability in RRMS patients according to healthy controls. In correlation analysis, there is statistical positive correlation between left eye P100 latency and TMT Part B time of completion ( $p=0.046$ ) besides, there is statistical negative correlation between right eye P100 latency and forward DST ( $p=0.04$ ). In conclusion, RRMS patients are encountering impairments in verbal memory processes, attention, retain of attention, working memory, visuospatial functions, executive functions, and construction ability. Although it is difficult to make any interpretation about whether there is any association between VEP abnormalities and cognitive disorder or not, the presence of a correlation between P100 latency and impairment in attention, short-term memory and executive functions are remarkable. Further studies about this subject are needed to encourage these findings.

### Disclosure

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### EP1570

#### Visual evoked potentials with low-contrast stimuli in the evaluation of optic neuritis

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**Background:** Contrast vision is known to be more sensitive to detect optic neuritis (ON) in patients with multiple sclerosis (MS). Even in the absence of a history of ON or decrease of visual acuity (VA), low-contrast VA may appear to be abnormal. Thus, we investigated if VEPs using low contrast stimuli which can reflect low-contrast VA would help to identify optic nerve involvement.

**Methods:** We studied 9 patients with demyelinating diseases (5 male, 4 female; 15-51 years old). We included patients with demyelinating diseases which were ON, MS, or neuromyelitis optica spectrum disorders. Patients who had an episode of ON within the last 6 months were excluded to minimize the effect of optic disc swelling by acute ON. Clinical characteristics including disease duration, history of ON, number of ON episodes, and Expanded Disability Status Scale (EDSS) scores were obtained. Monocular VEPs were induced using pattern-reversal checkerboard stimuli with 100% and 10% contrast at check size of 33 minute. For 10% contrast VEPs, a prolonged absolute latency (more than 130 ms which was a limit obtained from the previous literature) or absence of the P100 component was considered abnormal.

**Results:** Eleven eyes with ON and seven eyes without ON were evaluated. VEP latencies were significantly increased in response to low-contrast stimuli compared with high-contrast stimuli in both groups; low-contrast and high-contrast VEPs were  $136.1 \pm 19.5$  ms and  $115.3 \pm 14.4$  ms in the eyes of ON ( $p=0.004$ ) and  $134.5 \pm 12.4$  ms and  $103.3 \pm 4.6$  ms in the eyes without ON

( $p=0.001$ ), respectively. Low-contrast and high-contrast VEPs were abnormal in 66.7% ( $n=12$ ) and 27.8% ( $n=5$ ), respectively in all eyes ( $n=18$ ). Low-contrast and high-contrast VEPs were abnormal in 63.7% ( $n=7$ ) and 45.5% ( $n=5$ ) of ON eyes ( $n=11$ ). In the eyes without ON ( $n=7$ ), low-contrast VEPs detected subclinical involvement in 71.4% ( $n=5$ ), but high-contrast VEP did not find any abnormalities. Thus, low-contrast VEPs proved to be more sensitive to detect optic nerve involvement than high-contrast VEPs (McNemar  $p=0.016$ ) in the eyes of demyelinating diseases. Low-contrast VEPs latencies seems to be correlated with average RNFL thickness ( $p=-0.49$ ,  $p=0.063$ ), but not with VA ( $p=0.59$ ,  $p=0.833$ ).

**Conclusions:** In our study, we identified abnormal low-contrast VEPs in patients with demyelinating diseases, even when high-contrast VEPs is normal or no history of ON exists.

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Soo-Hyun Park: nothing to disclose

Nam-Hee Kim: nothing to disclose

## Neuropsychology

### EP1571

#### Validation of the French version of the BICAMS and comparison with the MACFIMS

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**Background:** The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) requires proper validation in each country.

**Objectives:** To establish French normative values in healthy subjects (HS) for the tests of the BICAMS and the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) and to determine the predictive value of the BICAMS to impairment at the MACFIMS in persons with multiple sclerosis (PwMS).

**Methods:** PwMS were recruited in several French centers. Healthy women and men, aged 18-64, without any known chronic systemic, psychiatric or neurologic disease or current dependence on alcohol or drugs, were recruited. All subjects were evaluated by trained neuropsychologists using the BICAMS and MACFIMS tests. The BICAMS includes the Symbol Digit Modalities Test (SDMT) and the first learning trials of the Brief Visual Memory Test Revised (BVMT-R) and the California Verbal Learning Test second edition (CVLT-II). A new form of the CVLT developed by Ehrle et al. has been used. The MACFIMS included the SDMT, the BVMT-R, the CVLT, the Paced Auditory Serial Addition Task (PASAT 3s), the Judgment of line orientation test (JLOT) the Controlled Oral Word Association Test (COWAT) and a French adaptation of the Dells-Kaplan sorting test, the "Epreuve de Classement des Cartes de Champagne" (ECCC, developed by Ehrle et al). ANOVAs were used to study the effects of age, education and gender for each test. Cognitive impairment (CI) was

diagnosed for each test and battery for patients with < 1.5 standard deviation (SD) of the HS group. The predictive value of CI at the BICAMS to CI at the MACFIMS was calculated using Bayesian statistics.

**Results:** 81 PwMS (27 primary progressive, 18 relapsing-remitting and 36 secondary progressive) and 253 HS have been included so far. Enrollment will end in June 2017. Normative values were calculated according to age, gender and education. ANOVA showed an effect of age on all tests except PASAT, COWAT and ECCC, an effect of education on all tests except BVMRT-R and an effect of gender on CVLT, PASAT and JLOT. In this preliminary analysis, 59% of 81 PwMS had CI at one test at least of the BICAMS and 37% at two tests at least of the MACFIMS. CI at the BICAMS (at least 1 test) predicts with a sensitivity of 93%, a specificity of 61% and accuracy of 73% CI at the MACFIMS (at least 2 tests).

**Conclusion:** The BICAMS could be more considered as a short cognitive assessment rather than a screening tool.

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### EP1572

#### Association between cytokine gene polymorphisms and cognitive functions in relapsing-remitting multiple sclerosis

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**Background:** Cognitive impairment is a common feature of multiple sclerosis (MS). There are still disputable questions about its morphological substrate and causation. The type and degree of cognitive dysfunction is not highly associated with disease course and physical disability, which emphasizes the need of disclosing the factors that determine the development of cognitive deficit.

**Objective:** The objectives of this study is to investigate the relationship between promoter polymorphisms -308A/G TNF-alpha, -1082A/G IL10 and -607C/A IL-18 and cognitive functioning in patients with relapsing-remitting MS (RRMS).

**Methods:** The study comprised 159 patients with RRMS, diagnosed according to McDonald's criteria (2010) in remission phase (mean age 40.08±8.48 years, mean disease duration 10.60±5.70 years) and 154 healthy controls matching by age, gender and education.

Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities test (SDMT) and Isaacs test were used for assessment of working memory, attention, visuo-perceptual abilities, information processing speed, verbal fluency and executive functions. Genotyping of the promoter polymorphisms in IL-10 and IL-18 was performed using ARMS-PCR assay, while polymorphism in TNF-alpha was genotyped by RFLP-PCR assay.

**Results:** Patients had lower mean score on all three neuropsychological tests than the controls ( $p < 0.0001$ ). In the patients' group the following significant associations were found: AG genotype of -308A/G TNF-alpha was associated with higher serum TNF-alpha concentration than GG genotype ( $p = 0.04$ ), higher serum TNF-alpha levels correlated with poorer attention and visuo-perceptual abilities (SDMT) ( $p = 0.033$ ); CC genotype of -607C/A IL-18 was related to lower score on the test for verbal fluency and executive functions (Isaacs test) as compared to AC variant ( $p = 0.04$ ).

The test result was considered abnormal when the patient scored 2 standard deviations below the average performance of the control group. Carriers of AA genotype of -1082A/G IL-10 from the patients' group showed significantly higher risk for abnormally low performance on PASAT than GG carriers ( $OR = 10.0$ ;  $p = 0.0471$ ).

**Conclusion:** The results of our study suggest that cytokine gene polymorphisms are one of the factors that affect cognitive functions in patients with RRMS. In Bulgarian population two promoter polymorphisms in pro-inflammatory cytokine genes - IL-18 and TNF-alpha, are associated with cognitive decline in RRMS patients.

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### EP1573

#### The executive component of naming ability in multiple sclerosis

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**Background:** Recent studies show language dysfunctions in Multiple Sclerosis (MS) at the level of the lexical access to the word in naming tasks. The presence of executive dysfunctions in MS has been demonstrated and confirmed through many studies. The link between executive component and the lexical access in naming task remains to be demonstrated.

**Objective:** Investigate the role of executive dysfunctions on naming abilities in MS.

**Method:** 105 patients ran the Boston Naming test (BNT) and the BCCog (a French short cognitive battery specific to MS). They were 2 Clinically Isolated Syndrome (CIS), 1 Radiologically Isolated Syndrome (RIS), 68 Relapsing Remitting, 28 Secondary Progressive (SP), and 6 Primary Progressive (PP) forms of MS. 68 women, 37 men, with a mean age of 46 years (ET: 13.24, 19-80), a mean study level of 12 years (ET: 3.6), and a median EDSS



score of 3.5 (0-8). 48 out of these patients also ran the Trail Making Test (TMT) and the Stroop test in order to evaluate respectively mental shifting and inhibitory control (2 CIS, 37 RR, 5 SP, 4 PP): 36 women, 12 men, with a mean age of 43 years (ET: 14.1, 19-74), a mean study level of 11 years (ET: 1.9), and a median EDSS of 3 (0-7.5).

**Results:** The results from the whole cohort confirm a lexical access deficit in MS on naming task. In the line of previous research the total score at the BNT is normal (mean: 53.57, SD: 6), but the patients need high number of phonological clue (mean 6, SD: 4) in order to normalize their scores. They were no significant correlation between the BNT and the BCCog scores. The lexical access deficit was stronger in the SP than in the RR forms of MS (ANOVA:  $f=4.4$ ,  $p < 0.5$ ). On the smaller cohort, linear regression analysis showed a significant impact of the speed processing at the TMTA ( $f=5$ ,  $p < 0.5$ ), the TMTB ( $f=13$ ,  $p < 0.001$ ), and of the mental shifting TMTB-A ( $f=9$ ,  $p=0.005$ ) on the lexical access. The production of phonological and semantic paraphasias was also impacted by the mental shifting ( $f=6$ ,  $p=0.02$ ). No naming score were linked to the inhibitory control score.

**Conclusions and perspectives:** The impact of executive dysfunction in MS on naming ability is enlightened through this study specifically at the level of mental shifting. It suggests the necessity to take executive dysfunction into account in order to permit an adequate reeducation of naming abilities in MS. Further studies will investigate the naming and executive functions at earlier state of the disease.

## Disclosure

Joly, Cohen & Lebrun: Nothing to disclose

## EP1574

### Cognitive profiles in multiple sclerosis: beyond information processing speed

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**Background:** Changes in information processing speed (IPS) constitute the most important cognitive alteration in multiple sclerosis (MS). However, given the clinical and topographical variability of the disease, cognitive alterations may vary greatly and appear in other forms in addition to slower IPS. Our aim was to determine the principal cognitive domains and components involved in MS and identify factors associated with presence of cognitive impairment in these patients.

**Methods:** Cross-sectional study of 311 patients with MS (236 with relapsing-remitting MS [RRMS], 52 with secondary progressive MS [SPMS], and 23 with primary progressive MS [PPMS]). Patients' cognitive function was assessed with a comprehensive neuropsychological assessment protocol. We conducted a principal component analysis to detect different cognitive patterns by identifying clusters of tests highly correlated to one another.

**Results:** Cognitive impairment was detected in 41.5% of the sample and more frequent in patients with SPMS and PPMS

( $P=0.002$ ). EDSS scores and education were independent predictors of cognitive impairment. Principal component analysis identified 7 clusters: attention and basic executive function (including IPS), planning and high-level executive function, verbal memory and language, executive and visuospatial performance time, fatigue-depression, visuospatial function, and basic attention and verbal/visual working memory. Mean scoring of components 2 and 3 was higher in patients with RRMS than in those with PPMS (component 2) and SPMS (component 3).

**Conclusions:** MS is linked to multiple cognitive profiles and alterations in different domains. This suggests that cognitive alterations in MS are heterogeneous and affect other domains in addition to IPS.

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## EP1575

### The relationship between attention impairment and information processing speed in patients with multiple sclerosis

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Multiple sclerosis (MS) is the most common autoimmune disorder in adulthood affecting the central nervous system which leads to significant physical disabilities (e.g. Noseworthy et al., 2006) and diverse cognitive deficits with respect to memory, processing speed, executive functions or attention and concentration (e.g. Ferreira, 2010). Due to the fact that attention impairment in MS seems to be related to the slowing down of information processing (Balsimelli et al., 2007) the aim of the present study is to examine this relationship using three different psychometric tests of selective attention.

The sample consisted of 38 patients with MS (42% men, 58% women) aged between 22 and 65 years ( $M=40.6$ ;  $SD=9.7$ ), and 38 age, gender and education matched healthy controls. Mean disease duration was 11.2 years ( $SD=6.2$ ), the type of MS was relapsing remitting in 92% and secondary progressive in 8% of the cases ( $EDSS-M=1.5$ ).

Results showed a significantly lower performance of patients with MS ( $M=34.63$ ,  $SD=16.22$ ) than healthy controls ( $M=27.26$ ,  $SD=10.49$ ;  $t=2.44$ ,  $df=37$ ,  $p=.019$ ) regarding basic selective attention skills in terms of psychomotoric speed (Trail Making Test - A). However, no significant differences between MS-patients and control subjects with respect to the number errors were found. With respect to selective attention in terms of discrimination of similar visual stimuli under time pressure (d2-Test of attention) a significant difference regarding concentration performance ( $t=-2.57$ ,  $df=37$ ,  $p=.014$ ) in terms of lower performance scores of

MS-patients ( $M=142.84$ ,  $SD=36.08$ ) than controls ( $M=162.26$ ,  $SD=38.43$ ) was found. No significant differences were found with respect to error rates. Significant differences ( $t=2.16$ ,  $df=37$ ,  $p=.037$ ) were found in selective attention ability in terms of inhibition of dominating stimuli (Color Word Interference Test) with MS-patients ( $M=77.47$ ,  $SD=16.92$ ) showing longer response times than controls ( $M=69.97$ ,  $SD=13.14$ ). Error rates did not differ significantly between MS patients and controls.

MS-patients showed lower performances than healthy controls with respect to different selective attention indices that rely on information processing speed. However, performance accuracy in terms of error rates did not differ between patients and controls. This result supports the suggestion that attention impairment in MS is mainly related to the slowing down of processing speed (Balsimelli et al., 2007).

### Disclosure

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### EP1576

#### Adaptive coping interventions should be a priority for people with multiple sclerosis and cognitive impairment

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**Background:** Lower quality of life (QoL) experienced by people with multiple sclerosis (PwMS) may be influenced by their coping style. Coping has been shown to provide an indirect link between cognition and stress, depression and anxiety in MS. This research extends this to the assessment of coping as a moderator or mediator between executive function and QoL in PwMS.

**Methods:** Participants were 107 people with relapsing remitting (83) or secondary progressive (24) MS (mean age:  $48.8 \pm 11.1$  years), administered executive function tasks (Symbol Digit Modalities Test, Word List Generation, Reading Span, Trail Making Test [TMT], Elevator Counting with Distraction, Visual Elevator, Modified 6 Elements, Zoo Map, Action Programming), transformed into Z-scores and totalled to provide an executive function index. Self-reported dispositional coping (COPE) and QoL (MS Quality of Life-54) inventories were also administered.

**Results:** Coping strategies mediated (behavioural disengagement, acceptance, growth and religion) and moderated (denial, active and total coping) the relationship between executive function and QoL in PwMS. Lower executive function indirectly increased mental health and overall QoL through acceptance, growth and

religion coping ( $SD$  range between .06 and .24 increase for each unit decrease). Whereas mental health QoL decreased with each executive function unit decrease, through the indirect effect of behavioural disengagement coping ( $SD=.14$ ). In participants who endorsed high denial coping, lower executive function was related to lower mental health and overall QoL ( $\Delta R^2=.07$  and .04 respectively), while this was not the case in participants who endorsed no-to-low use of denial coping. A relationship between lower executive function and lower physical health QoL was shown for participants who endorsed no-to-low active and total coping ( $\Delta R^2=.07$  and .04 respectively), which was not seen in moderate-to-high users of these coping strategies.

**Conclusion:** These results imply that in PwMS who have reduced executive function, less cognitively demanding adaptive coping strategies: acceptance, growth and religion, are related to increased QoL, while maladaptive strategies: behavioural disengagement and denial, are associated with poorer QoL. Interventions aimed at reducing avoidant coping strategies and increasing less cognitively demanding adaptive coping strategies in PwMS who experience deficits in executive function are required as a priority.

### Disclosure

The authors have nothing to disclose.

### EP1577

#### Interpretability of the patient-reported multiple sclerosis neuropsychological screening questionnaire: a cognitive screening tool?

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**Background:** Detecting cognitive impairment among patients with multiple sclerosis (MS) is relevant, given the profound impact of cognitive impairment on quality of life. A potential screening tool for cognitive impairment is the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ). However, the interpretability of its patient-reported version (MSNQ-P) is unclear.

**Objectives:** This study aimed to increase the interpretability of the MSNQ-P by (1) determining the optimal cut-off score to predict cognitive impairment among MS patients, and by (2) investigating which factors predict patient-reported cognitive problems.

**Methods:** A cohort of 335 MS patients completed the Dutch version of the MSNQ-P and a neuropsychological examination. Patients were classified into cognitively impaired (CI;  $n=87$ ), mildly cognitively impaired (MCI;  $n=107$ ) and cognitively preserved (CP;  $n=141$ ), based on the scores of 88 healthy controls. The optimal cut-off score to detect CI and MCI was considered the value for which [sensitivity + specificity] was highest. Furthermore, backward prediction models were used to determine which factors (cognition, depression, anxiety, fatigue, age, disease duration, education and physical disability) predict the MSNQ-P scores. Patients with scores on each factor were included in these analyses ( $N=244$ ).

**Results:** Preliminary results demonstrated a value of 20 as the optimal cut-off score to detect MS patients with CI (sensitivity = .60, specificity = .57, accuracy = .58), and 12 to detect MS patients with MCI (sensitivity = .82, specificity = .41, accuracy = .59). The MSNQ-P was predicted by the following factors: cognition, depression, anxiety, fatigue, education and physical disability, of

which fatigue was the strongest predictor. The model explained 49 percent of the variance on the MSNQ-P.

**Conclusion:** Due to low psychometric properties, the MSNQ-P cannot solely be used as a screening tool to detect cognitive impairment among MS patients, which is in line with previous studies. Multiple factors influenced patient-reported cognitive problems, including fatigue, depression, anxiety, cognition, education and physical disability.

### Disclosure

I.M. Nauta has received a grant from the Dutch MS Foundation.

L.J. Balk reports no conflict of interests.

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B.M.J. Uitdehaag has received personal compensation for consulting from Biogen Idec, Genzyme, Merck Serono, Novartis, Roche and TEVA.

B.A. de Jong has received speaker and consulting fees from Merck-Serono, Biogen, TEVA, Genzyme and Novartis.

### EP1578

#### Cognitive-motor interaction in patients with multiple sclerosis

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**Background:** Multiple Sclerosis (MS) patients, usually show cognitive and motor deficits. These deficits are regularly assessed separately, however recent studies have found an interaction when these tasks are performed simultaneously (Cognitive-Motor Interaction, CMI). The research in CMI allows a more ecological approach to the description of MS symptoms.

#### Objectives:

- 1) To compare performance in CMI between MS patients and healthy controls.
- 2) To analyze the relationship between CMI and clinical variables and cognitive impairment.

**Methods:** Forty patients with relapsing-remitting MS and 20 healthy controls were included. Patients age:  $38.03 \pm 11.26$ ; education:  $13.55 \pm 2.74$ ; Expanded disability status scale (EDSS):  $2.02 \pm 0.93$ ; Disease evolution:  $10.81 \pm 11.19$ . Controls age:  $34.00 \pm 14.25$ ; education:  $14.92 \pm 2.15$

Outcome measures:

**Clinical variables:** EDSS; Fatigue Severity Scale; Beck's Depression Inventory II.

**Cognitive variables:** BICAMS Battery;

**Dual tasks:** Two cognitive-motor interaction tasks (walking while performing verbal fluency/counting). The measure of the difference between subject performance in the simple task and in the situation of dual task was obtained. It was quantity: time, number of steps and cognitive performance.

**Results:** No significant differences were found between patients and controls in age ( $p=.268$ ) and education ( $p=.083$ ). Significant differences were found between patients and controls in CMI, in the time (fluency:  $p=.027$ ; counting:  $p=.038$ ), the steps of the counting task ( $p=.029$ ) and in the performance of both cognitive tasks (fluency:  $p=.040$ ; counting:  $p=.001$ ). Significant

correlations were found between CMI time and disease evolution ( $p=.025$ ), number of steps and physical disability ( $p=.042$ ), and between fluency and fatigue ( $p=.026$ ). No correlations were found between CMI and depression. There were no differences in CMI between patients with and without cognitive impairment.

**Conclusions:** Patients with MS show alterations in cognitive-motor tasks. Patients with more years of evolution, disability and fatigue evidence a worse performance.

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Garcea O.: Nothing to disclose

### EP1579

#### Functional MRI of the symbol digit modalities task in relapsing remitting multiple sclerosis

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**Background:** The symbol digit modalities task (SDMT) is recommended for assessing cognitive disabilities in multiple sclerosis (MS). There is a broad literature about adaptations of cognitive tasks (like the paced auditory serial addition task) for functional MRI, but only a few studies investigated the SDMT in both patients and healthy controls (HC).

Here, we adapted an oral version of the SDMT for fMRI to study the cognitive networks involved in the SDMT in both patients and healthy controls.

**Methods:** In total, 20 patients with relapsing remitting MS (EDSS 1-8; median 2.0) and 20 healthy controls, matched due to age (mean 41y) and gender (10 female) were investigated. Study design was an oral version of the SDMT with 30 sec blocks of assigning numbers to symbols.

**Results:** Both patients and healthy controls had strong functional activation in areas involved in language processing (Brodmann area (BA) 22), working memory (BA9), motor (BA4, BA6), visuomotor (BA7) and visual function (BA17-19) at  $p(\text{FWE}) < 0.05$ . Patients did not have any increased activation compared to healthy controls (MS>HC). Interestingly, HC had increased activation in BA 22 and in the insula (BA13) compared to the patients group (HC>MS).

**Discussion:** Here we could demonstrate a robust fMRI adaptation of the SDMT task. In our data, controls had an increased activation in language processing areas, indicating a disrupted network in MS-patients involved in this task.

### Disclosure

MG has received research grants and travel support from TEVA pharma, Biogen Idec, Sanofi genzyme and Novartis.



**EP1580****Cognitive impairment in neuromyelitis optica and multiple sclerosis**

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**Introduction:** Cognitive impairment (CI) has a growing interest among multiple sclerosis (MS) yet cognitive dysfunction is not as well characterized in neuromyelitis optica (NMO) seropositive for APQ4-IgG, even less is known for the MOG-IgG seropositive group. Our aim is to investigate the prevalence and patterns of cognitive impairment in our NMO and MS patients compared to matched healthy controls (HC).

**Methods:** We included 68 subjects in the study (5 NMO-AQP4, 4 NMO-MOG, 37 MS and 22 HC in a single centre. Cognitive function was evaluated with the Brief Neuropsychological Battery for MS, a Spanish validated battery for MS. Depression and fatigue assessments were conducted. Clinical and MRI data was also collected for the NMO/MS patients. CI was considered when a patient had 2 or more tests with a score under fifth percentile of HCs.

**Results:** Both NMO and MS groups performed worse than HC in all cognitive functions evaluated ( $p < 0.05$ ) including verbal memory, information memory speed, complex attention and verbal fluency. CI was detected in 22.2% of NMO and 13.5% of MS patients. Any abnormal test was observed in 22.2% of NMO and 40.5% of MS patients. CI in MS was related to EDSS score  $> 4$  and higher T2 load in brain MRI. The NMO patients with CI were 1 NMO-AQP4 and 1 NMO-MOG, no relation with clinical or radiological variables. No differences were found across 3 groups in terms of age, sex, education, depression or fatigue. We neither found differences in disease duration, time to treatment, time from last relapse, EDSS score or percentage of DMT between NMO and MS patients.

**Conclusions:** Both NMO and MS have worse cognitive performance than matched healthy controls. Our results support the need to evaluate cognitive function in both NMO-AQP4 and NMO-MOG patients to define the CI profile in these patients.

**Disclosure**

The authors of this study have nothing to disclose.

**EP1581****Executive functioning and delayed verbal memory retrieval in patients with multiple sclerosis**

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**Introduction:** It has been postulated that 40% to 60% of people with multiple sclerosis (MS) have memory and learning problems.

Training of executive functions has demonstrated to be effective for memory and learning rehabilitation (Mitolo, 2015).

**Objectives:** We aim to analyse differences between immediate recall and long term retrieval in patients with (MS) using Spanish Version of California Verbal Learning Test (TAVEC) and its relationship executive functioning (EF).

**Method:** 143 patients with remitting-relapsing MS (RRMS) were recruited from the clinic (mean age: 42,39 y.o.) and a sample of 35 healthy controls (HC) of the same age and educational level. A complete neuropsychological assessment was administered to both groups. MS sample was classified in three groups: no cognitive impairment, mild cognitive impairment and moderate cognitive impairment. We analyse differences between immediate and delayed retrieval in TAVEC in the HC and MS and the relationship with verbal fluency as a measure of EF.

**Results:** All MS groups obtained significant better ( $p < 0.01$ ) outcomes in long term retrieval than in short term retrieval; no significant differences were found in HC ( $p < 0.05$ ). A positive correlation ( $p < 0.01$ ) was found between phonological verbal fluency and memory in TAVEC for patients group.

**Conclusions:** MS patients obtain better delayed retrieval outcomes than in immediate memory. Verbal fluency is related to short and long term verbal memory in patients with multiple sclerosis and could explain the findings in TAVEC results. We suggest that patients with deficit in executive functioning take benefit of the semantic classification provided by this test what facilitates coding. Our results support previous research suggesting that EF are related to memory outcomes in patients with MS.

**Disclosure**

García-Vaz, F; Meca-Lallana, V; Palmi-Cortés, I; del Río Muñoz, B; Vivancos, J; Martínez-Ginés, M.L; García-Domínguez, J.M; Cuello, J.P; Romero-Delgado, F; Higuera, Y. have received speaker honoraria and/or travel grants from Novartis, Biogen, Gencyme, Almirall, Bayer, Teva, Roche. A. Rafael G. Gonzalez-Cuenca and Ariana Meldaña-Rivera has nothing to disclose

**EP1582****Cognition and the cerebellum in multiple sclerosis (MS)**

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**Background:** Cerebellar motor symptoms mean poor prognosis in MS and have been associated with a specific cognitive profile. A few studies have reported further dysfunction in the domains of reduced information processing speed (IPS), impairments in visuospatial functions and verbal fluency deficits associated with cerebellar damage. The cerebellum can encode models of sensory stimuli, providing mental representations of the world used to plan motor actions. Motor planning may be a key factor in the disability that cerebellar involvement imposes.

**Aim:** To explore how the cognitive profile of those with cerebellar motor symptoms (RR-MSc) differs from those without

cerebellar symptoms (RR-MSnc), and how this relates to motor function and motor planning.

**Method:** RR-MSc allocation was based on the NARCOMS tremor and coordination scale ( $\geq 4$ ). 21 HC

(10 males,  $\bar{x}$  age: 37.1), 21 RR-MSnc (6 males,  $\bar{x}$  age: 39.8) and 14 RR-MSc (7 males,  $\bar{x}$  age: 40.6) completed BICAMS (CVLT-II, SDMT, BVMT-R), PASAT3, and word list generation (WLG). We computed a cognitive impairment index (CII), and designated "widespread cognitive impairment" ( $\bar{x}$ - ( $>1.5SD$ ) on three or more tests). The 9-hole peg-test (9-HPT, as a sensorimotor control) and grooved pegboard test (GPT, more motor planning demands) were subtracted to compute a motor planning index (MPI).

**Results:** One-way ANCOVAs, covarying premorbid IQ revealed differences: SDMT ( $F(3,52) = 7.81, p < .001$ ), CVLT-II ( $F(3,52) = 3.42, p = .0024$ ), BVMT-R ( $F(3,52) = 2.93, p = .0042$ ), PASAT3 ( $F(3,52) = 12.89, p < .001$ ), CII ( $F(53,2) = 8.85, p < .001$ ), 9HPT ( $F(3,52) = 20.04, p < .001$ ), GPT ( $F(3,52) = 20.15, p = .001$ ), MPI ( $F(3,52) = 16.75, p < .001$ ). No differences were found for WLG ( $F(3,52) = 2.55, p = .07$ ). SDMT, GPT, 9HPT and MPI were the only tests to differentiate RR-MSnc and HC, and all tests differentiated RR-MSnc and RR-MSc other than WLG (not significant) and BVMT-R (just HC from RR-MSc). CII differed significantly between RR-MSc and all groups, but not between RR-MSnc and HC. RR-MSc showed significantly greater CII. Frequency of widespread cognitive impairment was 4.8% for HC, 28.6% for RR-MSnc and 57.1% for RR-MSc.

**Conclusion:** RR-MSc had more significant and widespread impairments than RR-MSnc, specifically with IPS, visual/verbal memory, and motor planning and function. These findings have clinical implications for those with cerebellar symptoms. MPI has potential as a clinical and research measure of motor planning.

## Disclosure

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## EP1583

**Resilience matters in multiple sclerosis: the independent contribution of psychological resilience to disability**

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**Objective:** To identify relationship between psychological resilience and measures of disability in patients with Multiple Sclerosis (MS).

**Background:** Resilience is a dynamic process encompassing positive adaptation within the context of significant adversity. Resilience facilitates healthy coping skills and thus improves quality of life. Despite the importance of this concept, resilience has been understudied in patients with MS. In this project we

analyzed whether greater resilience is associated with lower MS disability, independently of demographics (age, sex, education), cerebral atrophy, anxiety and depression.

**Methods:** Patients with early MS (87 RRMS, 18 CIS;  $< 5$  years diagnosed; median EDSS = 1.0) completed the Connor-Davidson Resilience Scale 10 item (CD-RISC-10): a well-established measure of psychological resilience. Disability was assessed with the MS Functional Composite (MSFC), which assesses upper extremity function (Nine Hole Peg Test, NHPT), gait (Timed 25 Foot Walk, T25FW), and cognition (Symbol Digit Modalities Test, SDMT). Cerebral atrophy was estimated with normalized brain volume and thalamic volume from 3D T1 3.0T MRIs. Mental Health Inventory assessed anxiety and depression. Any outliers were winsorized. We evaluated partial correlations between resilience and disability (MSFC, NHPT, T25FW, SDMT), controlling for demographics and cerebral atrophy. We then repeated analyses also controlling for anxiety and depression.

**Results:** Higher resilience was linked to lower disability on the MSFC ( $r_p = .281, p = .005$ ), and components SDMT ( $r_p = .279, p = .005$ ) and NHPT ( $r_p = .252, p = .012$ ), but not T25FW ( $r_p = .037, p > .50$ ). The independent contributions of resilience to lower disability on MSFC ( $r_p = .222, p = .028$ ), SDMT ( $r_p = .224, p = .026$ ), and NHPT ( $r_p = .236, p = .019$ ) remained when also controlling for anxiety and depression. In contrast, MSFC was unrelated to anxiety ( $r_p = .071, p = .487$ ) and depression ( $r_p = .069, p = .500$ ) when controlling for aforementioned covariates and CD-RISC-10. Resilience was unrelated to all demographics (e.g., education) and cerebral atrophy ( $P_s > .10$ ).

**Discussion:** We report a contribution of higher resilience (CD-RISC-10) to lower disability in MS, even independently of anxiety and depression. Lack of association between CD-RISC 10 and potentially confounding factors (cerebral atrophy, education as a proxy for socioeconomic status) strengthen our findings. Further studies are needed to examine whether higher resilience protects longitudinally.

## Disclosure

S. Klineova has given non-promotional lectures with Biogen Idec.

M. Fabian, G. Pelle, C. Lewis and J.F. Sumowski have nothing to disclose.

## EP1584

**The brief international cognitive assessment for multiple sclerosis (BICAMS): normative values with gender, age and education corrections in the Portuguese population with multiple sclerosis**

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**Background:** The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is an international assessment tool for monitoring cognitive function in multiple sclerosis (MS) patients. BICAMS consist of three tests: the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test - Second Edition (CVLT II) and the Brief Visuospatial Memory Test - Revised

(BVM-T-R). Our objective was to validate and assess the reliability of BICAMS to obtain normative data in Portuguese population.

**Method:** The sample composed of 107 MS patients and 62 healthy controls (HC). In order to test its reliability, BICAMS was re-administered in a subset of 25 patients after 3 month later. Depression, anxiety and fatigue were assessed by Hospital Anxiety and Depression Scale and Modified Fatigue Impact Scale (MFIS).

**Results:** The sample comprises a control group (n=62, age:  $M = 37,00$ ;  $DP = 12,74$ , education:

$M = 14,53$ ;  $DP = 3,44$ ) and a clinical group (n=107, age:  $M = 38,50$ ;  $DP = 11,34$ , education:  $M = 13,51$ ;  $DP = 3,82$ ). About 64% of the participants were women. The groups did not differ for age, education, or gender. The MS group performed significantly worse than the control group across the three neuropsychological tests, yielding the following values: SDMT:  $t(167) = 3.71$ ,  $p = .000$ ; CVLT-II:  $t(167) = 2.69$ ,  $p = .008$ ; and BVM-T-R:  $t(167) = 2.33$ ,  $p = .021$ . The mean raw scores for Portuguese normative data were as follows: SDMT:  $58.18 \pm 10.25$ ; CVLT-II:  $59.65 \pm 10.96$ ; and BVM-T-R:  $24.05 \pm 6.47$ . Finally, test-retest reliability coefficients for each test were as follows: SDMT:  $r = .92$ ; CVLT-II:  $r = .48$ ; and BVM-T-R:  $r = .86$ .

**Conclusion:** This BICAMS version is reliable and useful as a monitoring tool for identifying MS patients with cognitive impairment.

## Disclosure

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## EP1585

### Visual perceptual organization ability in multiple sclerosis

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**Objectives:** Cognitive impairment is recognized as a core feature of multiple sclerosis (MS). Mostly memory, attention, and executive functions are affected. This study aims to compare visual information processing between multiple sclerosis (MS) patients and controls.

**Methods:** A case-control study was conducted in 30 MS patients (22 female) and 30 (21 female) age-, gender- and education level-matched healthy subjects. All subjects were administered a detailed neuropsychological evaluation. Visuospatial information processing was evaluated with Hooper visual organization test (VOT), that requires perceptual and mental reorganization of parts of an object into an identifiable whole. The patients and controls were also administered Beck Depression Inventory and Mini-Mental State Examination.

**Results:** Patient and control groups did not differ in means of gender, age and education levels. BDI scores were similar in both groups and general cognitive functioning of patients were much the same.

MS subjects performed more poorly on the TMT part A and B than the control group. Mean scores obtained in PASAT were also lower in MS patients in comparison to healthy subjects. Visual perceptual organization ability of multiple sclerosis patients were much the same as controls' (MS:  $22.0 \pm 4.1$ , Control:

$1: 23.6 \pm 2.7$ ;  $p = 0.080$ ). In order to evaluate whether the progressing age does load any burden to visual perception organization ability, patient and control groups were categorized into three age groups (those younger than 25 years old, those between 25-35 years old, and those older than 35 years). Though, healthy controls showed no statistically significant difference between groups ( $F = 1.559$ ;  $p = 0.229$ ); a significant difference was observed in MS group ( $F = 4.670$ ;  $p = 0.018$ ). Especially those older than 35 years had a poor performance in comparison to younger patients. VOT performance showed a moderate inverse correlation with disease duration and total attack number ( $r = -0.471$ ,  $p = 0.009$ ;  $r = -0.451$ ,  $p = 0.012$ ; respectively) but no significant correlation with EDSS ( $r = -0.276$ ;  $p = 0.140$ ). VOT performance correlated moderately with PASAT score ( $r = 0.529$ ;  $p = 0.005$ ) and showed an inverse correlation with TMA-A, -B scores ( $r = 0.535$ ,  $p = 0.002$ ;  $r = -0.421$ ,  $p = 0.021$ ; respectively).

**Conclusions:** Visual information processing ability is unimpaired in MS patients.

## Disclosure

Serpil Demirci: nothing to disclose

## EP1586

### Neuropsychological Management of multiple sclerosis: Evaluation of the added value of a supervised and customized cognitive rehabilitation program for self-used at home

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**Background:** Cognitive and affective dysfunction negatively impact daily living of patients, particularly quality of life (QoL). Pharmacological treatment did not demonstrate any effect on cognition compared to cognitive rehabilitation (CR) programs that show promising results but are less consistent concerning affective and QoL domains.

**Objective:** We developed a randomized controlled study to demonstrate the interest of a patient's tailored computerized CR program, conducted at home, on QoL and self-esteem (SE).

**Methods:** This project comprises two phases. First, we conducted a pilot study on 10 multiple sclerosis (MS) patients to assess the feasibility and acceptance of this project. 41 computerized exercises were further selected according to the specificity of MS cognitive difficulties and appropriate recommendations of patients. The second step will consist of the randomized study conducted with two groups (the experimental group and the control group). The experimental group will benefit for the CR program and a psychological support at home during eight weeks (3 sessions exercises of 45 minutes per week) whereas the control group will only receive psychological support. QoL and SE, respectively assessed by the MUSIQOL and the SE-inventory questionnaires, will be evaluated three times (at baseline, after the CR program and 6 months after the CR program). Given the expected MUSIQOL score variation, inclusion of 18 patients per group will be required.

**Results:** Pilot-study showed high acceptance and feasibility of exercises as well as improved subjective QoL. Preliminary results of the randomized study will be presented at the meeting.



**Conclusion:** As QoL and SE are poorly evaluated in CR studies, we believe that this original customized CR program will highlight the benefits on both parameters over short and longer delays in patient's daily life.

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### EP1587

#### Cortical lesions correlate with cortical atrophy and drive cognitive impairment in multiple sclerosis

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**Background:** There is increasing scientific data that cortical lesions (both number and size) are an independent factor in the pathogenesis of cognitive impairment in multiple sclerosis (MS). Several studies have also linked cortical lesions with disability and evolution to secondary progressive phase of the disease.

**Objective:** Our study aims to investigate the role of cortical lesions, cortical atrophy and white matter lesions in cognitive decline in patients with MS.

**Methods:** Fifteen patients with MS underwent clinical, detailed neuropsychological and neuroimaging examination. We performed a 3 Tesla magnetic resonance imaging with three-dimensional double inversion recovery in the sagittal plane added to the standard protocol. The images were reviewed and compared by two radiologists. Lesions were divided into 6 groups and the stage of cortical atrophy was assessed on a scale of 0-4.

**Results:** Cortical lesion pathology positively correlated with the severity of cortical atrophy ( $p=0.05$ ) and periventricular white matter lesion load ( $p<0.05$ ). Cortical lesions correlated with some cognitive scores including Mini-Mental State ( $p<0.05$ ), information processing, measured by Symbol Digit Modalities Test ( $p=0.05$ ) and verbal fluency ( $p<0.05$ ). White matter lesion load correlated with executive functioning, measured by the number of hits ( $p=0.001$ ) and omissions ( $p<0.05$ ) in the Paced Auditory Serial Addition Test and reached near statistical significance for recognition in the Free and Cued Selective Reminding Test ( $p=0.06$ ). Physical disability, measured by the Expanded Disability Status Scale, correlated with cortical atrophy ( $p<0.05$ ).

**Conclusion:** Our results show that cortical lesion pathology is one of the most sensitive imaging correlates of cognitive

dysfunction in MS. Specific tests measuring executive dysfunction may correspond to the different types of imaging pathology and their underlying pathogenic processes.

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### EP1588

#### Subjective versus objective cognitive screening of patients with multiple sclerosis

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**Background:** Cognitive impairment occurs frequently in the patients with multiple sclerosis (MS). However, the accuracy rate of subjective cognitive complaints for predicting of abnormal objective cognitive performance is lacking.

**Objectives:** To investigate the relationship between subjective cognitive complaints assessed by the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) and objective cognitive performance evaluated by the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).

**Methods:** A total of 1052 patients (70% females, at baseline: mean age:  $38.1\pm 8.8$ ; mean disease duration:  $9.6\pm 7.1$ ) after the first demyelinating event suggestive of MS or with clinically definitive MS were included in this 2-years longitudinal study. The MSNQ, the BICAMS battery and the Beck Depression Inventory (BDI) were evaluated at baseline and at 24 months. Pearson's and Spearman's correlation analyses were performed to evaluate the relationships among absolute values of the MSNQ, the BICAMS subtests and the BDI score. Sensitivity, specificity, accuracy and positive predictive value were used to assess agreement between the subjective and objective screening methods.

**Results:** At baseline, we observed a weak negative correlation ( $r=-0.273$  to  $-0.134$ ;  $p<0.001$ ) between absolute values of the MSNQ and the BICAMS subtests. The abnormal MSNQ (cut-off value  $>24$ ) at baseline identified patients with the abnormal BICAMS ( $\geq 1$  abnormal subtest) at baseline with 69% accuracy (sensitivity=33%, specificity=83%, positive predictive value [PPV]=41%). The MSNQ was also associated with the BDI ( $r=0.540$ ;  $p<0.001$ ). We observed a weak negative correlation between absolute values of the MSNQ at baseline and the BICAMS subtests at 24 months ( $r=-0.259$  to  $-0.117$ ;  $p<0.001$ ). The abnormal MSNQ at baseline identified patients with the abnormal BICAMS at 24 months with 64% accuracy (sensitivity=30%, specificity=82%, PPV=46%).

**Conclusion:** Subjective evaluation of cognitive performance assessed by the MSNQ predicted the abnormal outcome of objective cognitive screening by the BICAMS with only 64-69% accuracy. On the other hand, the abnormal MSNQ was associated with abnormal cognitive screening with a relatively high specificity

(82-83%). MSNQ is not suitable cognitive screening tool due to its low sensitivity (30-33%), however, subjective cognitive complaints of MS patients need to be taken seriously, because they are often associated with cognitive impairment or depressive symptoms.

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### EP1589

#### A cognitive occupation-based programme for people with multiple sclerosis (COB-MS): a study to test feasibility and clinical outcomes

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**Introduction:** Difficulties with cognition have been reported to be present in 50-60% of people with MS. Despite the high prevalence little has been done to address these difficulties and more importantly the impact that they have on a person's everyday life. The Cognitive Occupation Based Programme for People with MS (COB-MS) was developed to address this. The COB-MS focuses on rehabilitation that is measured by and taught through focusing on occupational participation.

**Objectives:** This feasibility study assessed the following outcomes -eligibility criteria, recruitment and retention, participant acceptability and; administration protocol.

**Method:** This feasibility study used an experimental, pre-test/post-test design with eight-week follow-up. Participants were recruited from MS networks using convenience sampling. Twelve participants (1 male) were recruited to two COB-MS groups, which consisted of eight sessions (2 individual, 6 group).

Participants were asked to complete various homework activities throughout the week in order to practice strategies learned and solidify learning.

**Results:** Results, from this modestly-sized sample, are promising with significant improvements seen in everyday life goal attainment [Goal Attainment Scaling; GAS ( $z = -2.67$ ,  $p < .008$ )], and memory, including verbal memory, visuospatial memory and self-reported everyday memory [CVLT-II ( $c^2$  (2,  $n = 9$ ) = 13.89,  $p < .001$ ), BVMT-R ( $c^2$  (2,  $n = 9$ ) = 11.09,  $p < .004$ ), and EMQ-R ( $c^2$  (2,  $n = 9$ ) = 7.00,  $p < .030$ )]. It was also well-received and adhered to by participants. Recruitment methods were explored and the protocol followed by three facilitators.

**Conclusion:** Significant improvements were observed in all daily life measures and most cognitive measures. Limitations include selection bias and subtle practice effects in cognitive measures. Preliminary data from a small sample looks promising and is encouraging to test the COB-MS on a larger sample of people with MS.

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### EP1590

#### Cognitive disorders in multiple sclerosis: a screening tool proposed in current practice. The experience of the Rhône-Alpes SEP Network

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**Introduction:** Cognitive disorders are common in Multiple Sclerosis (MS) and can be present at any stage of the disease, affecting attention, concentration, planning, memory. Their functional impact can alter quality of life. They are often associated with confounding factors: fatigue, anxiety, depression. The question of the optimal time for a more complete neuropsychological assessment remains to be asked, this assessment being most often carried out before a spontaneous cognitive complaint with the difficulty of determining the weight of any associated factors.

**Objectives:** The aim was to assess the feasibility and relevance of a rapid, comprehensive and functional cognitive screening battery, which could be carried out during an usual consultation.

**Methods:** 73 MS patients reporting a cognitive complaint benefited from cognitive explorations. Seven themes were studied through Visual Analogue Scales (VAS), quantified on 10 points: fatigue, fitness, pain, thymic state, attention, memory, organization. The cognitive study involved the realization of the SDMT and the story of Barbizet, completed by a fatigue scale (FSS score) and an anxiety and depression scale (HADS).

**Results:** A good feasibility of the evaluation was validated with a duration of 15 to 20 minutes, allowing a realization in common practice. Among the different dimensions explored through the VAS, a score >5 was identified for fatigue, fitness and memory. Fatigue was also underlined by the average FSS score (5.1/7). The HADS did not

appear pathological. As for the analytical evaluation, the mean score of SDMT was pathological at 38.9 (SD:13.6). The story of Barbizet showed an average score of 11.3 (SD:4.4). Interestingly, double dissociation was found for some patients between SDMT and recall performances, proving interest of both tests. Spearman's correlation found a modest correlation for pain, memory, state of mood and organization; on the contrary, the use of a purely analytical balance appeared insufficient. These results underline the value of jointly realizing these personal feelings scales and cognitive tests.

**Conclusion:** This work validates the use of a simple and reproducible tool in common consultation, in the detection of cognitive disorders and possible confounding factors, in the MS patients. These tests allow to refer patients for further explorations, to adjust the management of confounding factors and thus to optimize the management, in particular for fatigue and anxiety.

## Disclosure

Any disclosure for this work.

### EP1591

#### No evidence of disease activity and cognition in relapsing-remitting multiple sclerosis

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**Background:** The term "No evidence of disease activity" (NEDA) means no relapses or disability progression and no new/enlarging MRI lesions in relapsing-remitting multiple sclerosis (RRMS). Cognitive progression in these patients has been poorly studied.

**Objective:** Determine the cognitive evolution in NEDA patients.

**Method:** RRMS patients were examined at baseline and in the second evaluation (after a one to three years period) with neurological, neuropsychological and structural MRI examinations. Outcomes measures: Neuropsychological assessment: Selective Reminding Test (SRT), 7/24 Visuospatial Test, SDMT and Verbal Fluency, Beck Depression Inventory II (BDI II); Clinical measures: Expanded disability status scale (EDSS).

**Results:** 15 NEDA patients were described. Age: 37.5 13.9; Female: 8; education: 12.7 2.7 years; EDSS: 3.21.5; disease evolution: 9.18.3 years. When compare cognitive function between both neuropsychological evaluations, NEDA patients show significant low scores in verbal memory ( $p = .026$  and a trend toward worsening in verbal fluency ( $p = .056$ ).

**Conclusions:** In our work we have found cognitive changes in NEDA patients. Based on these results, the relevance of cognitive assessment as a marker of disease activity is reaffirmed.

## Disclosure

Nothing to disclose

### EP1592

#### Characteristics of verbal strategies used in semantic and phonemic fluency in patients with multiple sclerosis

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**Background:** Patients with multiple sclerosis (MS) exhibited deficiencies in the performance of verbal fluency tasks. However, most studies analysed mainly the number of correctly produced words in particular tasks' variants. Little is known about verbal strategies applied by patients that facilitate the performance of the described test.

**Objectives:** The characteristics of semantic and phonemic fluency as well as verbal strategies adopted by MS patients.

**Methods:** The study embraced 30 patients with diagnosed relapsing-remitting MS as well as 30 people without neurological diseases or mental disorders. Both groups matched for age, sex or number of years of education. Two versions of the Verbal Fluency Test were applied: semantic (names of animals) and phonemic (words beginning with K).

**Results:** In semantic fluency test MS patients obtained significantly lower results compared with the control group with regard to the following indicators: the number of correct answers, the number of clusters, the number of switches as well as the ratio of the number of switches to the number of correct answers. Similarly, patients demonstrated worse results in phonemic variant in the following parameters: the number of correct answers, the number of switches and the ratio of the number of switches to the number of correct answers. In turn, in semantic fluency patients obtained better results than healthy individuals for cluster's size and in phonemic variant in the ratio of the number of clusters to the number of correct answers. Medium effect sizes were demonstrated for three indicators and large ones for the other indicators. No significant inter-group differences were found for other measures.

**Conclusions:** Patients' lower results demonstrated in the ratio of the number of switches to the number of correct answers in both variants of the test as well as no differences found in the ratio of the number of clusters to the number of correct answers in semantic variant and, at the same time, better results of patients in this component in phonemic variant could suggest the dominance of disturbances in executive functions over the problems in the scope of semantic memory in these patients. However, the performance of both tasks could also be hindered by deficiencies in language functions and slower information processing.

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## Biomarkers

### EP1593

#### Adiponectin as a possible biomarker in multiple sclerosis

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**Background:** Among adipokines, adiponectin plays important roles in the regulation of energy homeostasis and insulin sensitivity, enough to be considered a marker for obesity and related diseases as type II diabetes. Moreover, an immunomodulatory action in several systemic inflammatory disorders has been demonstrated. Adiponectin is produced as a monomer that circulates in serum as different oligomers (LMW, MMW, HMW). Few studies analyzed the adiponectin role in a neuroinflammatory disorders as Multiple Sclerosis (MS) with controversial results. In this study, we analyzed serum adiponectin levels in MS patients and investigated the potential relationships with disease features.

**Methods:** 99 unrelated MS patients, diagnosed according to McDonald Criteria, from University of Campania “Luigi Vanvitelli”, and 87 age- and sex-matched controls were recruited. Anthropometric and biochemical features of MS patients and controls were evaluated and compared. In serum, adiponectin levels were measured by ELISA. Adiponectin oligomeric profile was characterized by Western blot.

**Results:** Serum adiponectin levels analyzed by ELISA assay were higher in MS patients compared to matched controls (12,18 vs 10,02 µg/ml) ( $p < 0,001$ ). A negative correlation was found between adiponectin levels and BMI in controls while a positive correlation was present in patients. No difference in adiponectin was found between active/no active patients and between forms of disease. Western blotting analysis performed on serum demonstrated that the HMW adiponectin oligomers are increased in MS patients.

**Discussion and conclusions:** Our study demonstrated a strong modulation of adiponectin and its HMW oligomers in MS. The positive correlation of adiponectin with BMI in MS patients suggests that adiponectin plays a role in the regulation of neuroinflammatory conditions as MS, probably acting towards pro-inflammatory pathways at the basis of MS. Further studies are required to better understand the biological role of adiponectin and its possible usefulness as a biomarker of MS.

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## EP1594

**Cerebrospinal fluid oligoclonal IgM bands and prognosis in multiple sclerosis patients: pooled long-term follow-up data**  
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**Background:** Cerebrospinal fluid (CSF) oligoclonal IgM bands (IgMOB) have been linked to a shorter first-inter attack interval and to a more aggressive disease course in Multiple Sclerosis (MS) patients. Some recent studies [1-2], however, did not confirm this data.

**Objective:** Aim of the study was to assess the prognostic role of CSF IgMOB over time and in relation to the introduction of disease-modifying drugs (DMD).

**Methods:** We pooled and updated information on patients included in previous studies on CSF IgMOB and divided them in two groups, depending on whether the disease onset had occurred before or in/after 1995, year in which the first DMD became available in Italy.

**Results:** We studied 336 patients (220F) who had carried out a spinal tap between 1984 and 2011 and who were followed up for a median of 13 years (IQR: 8-19) from onset. Ninety-one percent of patients with disease onset prior to 1995 (63/69) had not been treated in the first two years as opposed to 49% (131/267) of those with onset in/after 1995 ( $p < 0.001$ ). The presence of CSF IgMOB significantly increased the odds of reaching an EDSS of 3, 4 and 6 (OR: 4.7, 5.7 and 7.1, respectively) only in patients with disease onset prior to 1995.

**Discussion:** Our results may be explained by the efficacy of DMD in modifying the disease course, although we must point out that the older cohort carried out the spinal tap after a longer median interval from onset (12 months versus 1 month). IgMOB-positive patients in the older group may, therefore, hypothetically, be more likely to have persistent IgM responses (associated with lipid-specific IgMOB and a more aggressive disease course), while in the more recent cohort we may have included more IgMOB-positive patients with transient IgM responses.

**Conclusion:** CSF IgMOB were predictive of higher long-term disability only in patients with MS onset prior to the treatment era and with a longer onset-spinal tap interval.

1. Ferraro D, Galli V, Vitetta F, et al. (2015) Cerebrospinal fluid CXCL13 in clinically isolated syndrome patients: Association with oligoclonal IgM bands and prediction of Multiple Sclerosis diagnosis. *J Neuroimmunol* 283:64-9.
2. Frau J, Coghe G, Loreface L, et al. (2016) Intrathecal IgM synthesis: is really a prognostic factor? *Neurol Sci* 37:S260-1.

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## EP1595

**CSF neurofilament light chain provides a valuable prognostic tool in multiple sclerosis**

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The presence of elevated levels of neurofilament light chain (NFL) in the cerebrospinal fluid (CSF) is an indicator of axonal damage in the Central Nervous System (CNS) and has been tested as a biomarker in Multiple Sclerosis (MS). However, its value to predict disease course and to assist in therapeutic management still needs further confirmation.

In this study, our goal was to evaluate the usefulness of CSF NFL to predict disease severity in Relapsing-Remitting MS (RRMS) patients followed up to 10 years ( $6.5 \pm 3.3$  years).

The study population comprised 39 RRMS patients and a control group consisting of 17 patients with non-inflammatory neurological diseases. In RRMS patients, evidence of active disease during follow-up (EDA) was evaluated through the occurrence of relapses, brain magnetic resonance imaging MRI activity or EDSS worsening. All patients received immunomodulatory treatment during follow-up: 20 underwent first line treatments ( $\beta$ -Interferon and Glatiramer Acetate); while 19, with a more aggressive disease course, were submitted to second line therapies (Natalizumab, Rituximab and Fingolimod). CSF samples were collected at time of diagnosis and NFL baseline levels were measured using an ELISA kit (Uman Diagnostics AB, Sweden).

There were no significant differences between RRMS patients and controls neither regarding age nor gender, but NFL levels were significantly higher in patients ( $2532 \pm 2237$  vs.  $896 \pm 932$  pg/mL;  $p=0.0011$ ). Regarding RRMS patients, no correlation was found between baseline NFL levels and EDSS score at lumbar puncture (LP) or at follow-up. However, we found increased baseline CSF NFL levels in patients with EDA compared to those not showing signs of active disease ( $3129 \pm 2061$  vs.  $2048 \pm 2440$  pg/mL,  $p=0.038$ ). Moreover, patients submitted to second line treatment during follow-up, had significantly higher baseline CSF NFL levels than patients that only underwent first line treatment ( $3305 \pm 2496$  vs.  $1759 \pm 1680$  pg/mL,  $p=0.022$ ). In fact, in a logistic regression analysis (including age of onset, gender, IgG oligoclonal bands, disease duration, EDSS at LP), baseline NFL levels was the only variable that could significantly predict, with 84% accuracy, the need for undergoing second-line therapy ( $p=0.022$ ). This study demonstrates the potential prognostic value of baseline CSF NFL in RRMS baseline CSF and supports its use as a guiding tool for long-term management of the disease.

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## EP1596

**Principal component analysis of intrathecal chemokine expression in multiple sclerosis and other neurological diseases**

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**Background/goals:** Chemokine dysregulation contributes to immune dysfunction, inflammation and central nervous system (CNS) damage in multiple sclerosis (MS). Chemokines have diverse interactions with other chemokines and immune cells. We used principle component analysis (PCA) to unravel the interplay of a selection of chemokines for MS vs. other neurological diseases (OND).

**Materials/methods:** Matched serum and cerebrospinal fluid (CSF) samples from the Dartmouth Neurological specimen bank were obtained on 33 patients. Patients were chosen based on their diagnosis of MS ( $n=8$ ), other neuroinflammatory diseases (OND-I,  $n=8$ ), idiopathic intracranial hypertension patients felt to be negative controls (IIH,  $n=8$ ), and a variety of other non-inflammatory OND (OND-NI,  $n=9$ ). Forty chemokines were measured in CSF and serum samples using a multiplex bead array assay (BioPlex Pro-Human Chemokine Panel, BioRad). In order to compare intrathecal production of chemokines, CSF chemokines were normalized to serum chemokines by calculating a CSF/Serum ratio, which accounts for individual variability in serum concentrations as well as blood/CSF barrier integrity. Ratios were compared non-parametrically among groups. PCA was then used to summarize the overall patterns in chemokine expressions in MS vs. OND.

**Results:** We found differences in the average ratio of 6 of the 40 analyzed chemokines: MS patients had elevated CSF/Serum ratios of CXCL13, CXCL10, CXCL9, CCL1, CCL22, and MIF. However, the PCA revealed only increased CXCL13, CXCL10, CXCL9, CCL22, and CCL1 concentrations to be significantly associated with MS. Overall, 5 principal components (PC) were generated, with the first 2 PCs explaining 99.6% of the total variance in the chemokine data. PC1 reflects an activation of cell-mediated immunity due to its positive loading with both CXCL10 and CXCL9; conversely, PC2 reflects an activation towards humoral immunity due to its positive loading with CXCL13, CCL1, and CCL22.

**Conclusions:** Our findings suggest that mutually interacting cellular and humoral immune components modulate MS pathology and may contribute to the differential diagnosis of MS among patients with neurological conditions.

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## EP1597

**Lactate, beta2-microglobulin and ACE in cerebrospinal fluid as markers of clinical disease course and severity in patients with multiple sclerosis**

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**Background:** The increasing armamentarium of immunotherapeutics for multiple sclerosis (MS) calls for reliable biomarkers to better monitor disease activity, predict progression and evaluate treatment response in individual patients. CSF lactate, beta2-microglobulin and angiotensin converting enzyme (ACE) levels were all reported to reflect various aspects of MS disease activity which we validated in a large cohort of MS patients.

**Methods and results:** An automated search identified 554 patients with MS who received an analysis of CSF lactate, beta2-microglobulin and ACE levels as part of their routine diagnostic workup in our department between 2005 and 2012. Manual chart review allowed their classification as purely relapsing-remitting MS including cases of clinically isolated syndrome (RRMS, n=321), secondary progressive MS (SPMS, n=170) or primary progressive MS (PPMS, n=63) according to the 2010 revision of the McDonald diagnostic criteria. Patients were further characterized by EDSS score, disease duration, Multiple Sclerosis Severity Score (MSSS) and current relapse activity. We found that beta2-microglobulin was significantly elevated in CSF of patients with PPMS (mean 1.42 mg/l,  $p < 0.05$ ) and SPMS (mean 1.59 mg/l,  $p < 0.01$ ) compared to those with RRMS (mean 1.17 mg/l), while CSF levels of lactate and ACE did not differ between these three groups. In patients with stable but not in those with active RRMS (n=104 and n=217, respectively), we found a moderate positive Spearman correlation between both MSSS ( $r = 0.39$ ,  $p = 0.0023$ ) or EDSS ( $r = 0.41$ ,  $p = 0.0015$ ) and beta2-microglobulin in CSF. In contrast, CSF lactate weakly correlated with MSSS and EDSS in patients with active, but not in those with stable RRMS ( $r = 0.21$ ,  $p = 0.0035$ ;  $r = 0.16$ ,  $p = 0.026$ , respectively).

**Conclusions:** In our cohort, CSF beta2-microglobulin but not lactate or ACE levels were higher in chronic progressive than in relapsing-remitting MS patients, in whom in currently relapse-free patients a higher CSF beta2-microglobulin level correlated with higher disease severity and disability.

## Disclosure

Axel Haarmann, Luzia Hähnel, Michael Schuhmann, Guido Stoll and Mathias Buttmann have nothing to disclose.

## EP1598

### Cerebrospinal fluid levels of neurofilament light chain, C-X-C ligand motif 13, and chitinase-3-like protein 1 reflect distinct pathological processes in multiple sclerosis

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**Background:** Analysis of cerebrospinal fluid (CSF) biomarkers has the potential of clarifying the interplay between the inflammatory and degenerative components of multiple sclerosis (MS). The main goal of the study was to determine whether CSF concentration of neurofilament light chain (Nf-L), C-X-C ligand motif 13 (CXCL13), and chitinase-3-like protein 1 (CHI3L1) were associated with MRI measures of disease activity and grey matter pathology.

**Methods:** Consecutive patients with clinically isolated syndrome (CIS) or MS according to 2010 McDonald criteria, and a CSF sample stored at Verona Laboratory of Neuropathology were eligible for the study. All cases had a brain MRI performed at the time of lumbar puncture with a 1.5 Tesla scanner and a standardized protocol, including Double Inversion Recovery sequences. Brain volume analysis was performed using SIENAX software. CSF standard analysis, including IgG index and oligoclonal bands (OBs), was done at the time of sample collection. Commercial ELISA kits were used to determine Nf-L, CXCL13 and CHI3L1 levels on stored CSF samples. The distribution of CSF biomarker levels according to presence of enhancing and cortical lesions on brain MRI and the correlation between biomarkers CSF concentration, brain volumes and number of cortical lesions were analysed.

**Results:** As of May 2017, 78 patients (50 females) have been included in the study, with mean age at CSF collection of  $38.3 \pm 12.5$  years. 48 patients had relapsing-remitting MS, 15 a CIS, and 15 progressive forms of MS. Median disease duration at inclusion was 0.6 years (range 0-31). Mean Nf-L concentration was 4215 ng/L in patients with at least one enhancing lesion on MRI compared to 2043 ng/L in patients with no enhancing lesions ( $p = 0.002$ ). Mean Nf-L concentration was greater in patients with OBs or increased IgG index in CSF compared to cases without such findings (3795 vs. 1856 ng/L,  $p = 0.002$ ). Mean concentration of CXCL13 was 53.4 pg/mL in patients with OBs or increased IgG index in CSF, compared to 11.4 pg/mL in patients with no such evidence ( $p < 0.001$ ). Finally, CHI3L1 level was inversely correlated to total cerebral volume ( $r = -0.317$ ,  $p = 0.018$ ) and white matter volume ( $r = -0.279$ ,  $p = 0.039$ ).

**Conclusions:** Nf-L and CXCL13 levels in the CSF of MS patients are associated with MRI and CSF measures of inflammatory activity, while CHI3L1 CSF concentration is correlated to brain volume loss. Implications for prognosis and treatment deserve further investigation.

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## EP1599

### CSF cell signature and biomarkers of neuroinflammation and neurodegeneration in MS: preliminary results of the OBOE study

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**Background:** Development of cerebrospinal fluid (CSF) biomarkers, such as neurofilament light chain (NfL) and/or lymphocyte cell signatures, may improve current understanding of multiple sclerosis (MS) pathogenesis and the therapeutic mechanism of action (MOA) of disease-modifying treatment (DMT). Ocrelizumab is a humanised monoclonal antibody that selectively targets CD20, a cell-surface antigen expressed on pre-B cells, mature B cells and memory B cells but not lymphoid stem cells or plasma cells. The Ocrelizumab Biomarker Outcome Evaluation study (OBOE; NCT02688985) aims to further elucidate the MOA of ocrelizumab in patients with relapsing MS (RMS) and primary progressive MS (PPMS) by examining potential biomarkers of neuronal or glial injury, B-cell antigen presentation, immunoglobulin production, cytokine secretion and meningeal inflammation.

**Objective:** To elaborate on the blood and CSF biomarkers being studied and the methodology for determining CSF cell signatures in OBOE.

**Methods:** The open-label OBOE study is enrolling treatment-naïve or previously treated patients with RMS or PPMS. All patients initially receive two intravenous (IV) infusions of ocrelizumab 300 mg separated by 14 days; at Weeks 24 and 48, patients with PPMS repeat this regimen, while patients with RMS receive single 600-mg infusions. Lumbar punctures to obtain CSF are performed prior to and at Month 3, 6 or 12 of ocrelizumab treatment; longitudinal CSF samples are also being collected from a subset of RMS patients while on DMT prior to receiving ocrelizumab. Freshly isolated CSF cells are examined using a standardized cell-surface phenotyping flow cytometry assay. Primary endpoints include changes in NfL, CD19<sup>+</sup> B cells and CD3<sup>+</sup> T cells in the CSF over 3, 6 and 12 months of ocrelizumab treatment.

**Results:** Planned enrolment includes 88 patients with RMS and 16 with PPMS; updated information on patient disposition will be presented. Assay development and approach to standardization of the multicenter CSF flow cytometry assay to limit analytical variability will be discussed.

**Conclusions:** OBOE will provide important information on putative disease biomarkers in the blood and CSF of patients with RMS and PPMS and the effects of selectively depleting CD20<sup>+</sup> B cells on those markers. Findings are expected to improve understanding of the MOA of B-cell depletion in patients with MS.

## Disclosure

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**A.H. Cross** has served on scientific advisory boards for AbbVie, Biogen, EMD Serono, Race to Erase MS, Genentech/Roche, Genzyme/Sanofi, the Conrad N. Hilton Foundation, Mallinckrodt, Novartis and Teva.

**A. Bar-Or** has served on scientific advisory boards for F. Hoffmann-La Roche Ltd, Genentech, Inc., Biogen, GlaxoSmithKline, Merck/EMD Serono, MedImmune, Mitsubishi Tanabe, Ono, Receptos, Sanofi-Genzyme and Guthy-Jackson/GGF and has received research support from Novartis and Sanofi-Genzyme.

**A. Herman** is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd.

**D. Fiore** is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd.

**C. Harp** is an employee and shareholder of Genentech, Inc.

**B. Musch** is an employee and shareholder of Genentech, Inc.

## EP1600

### Neuronal and glial CSF biomarkers in patients with secondary progressive multiple sclerosis treated with dimethyl fumarate

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**Background:** Dimethyl fumarate (DMF) has been approved for the treatment of patients with relapsing forms of multiple sclerosis (MS). Investigation of DMF in secondary progressive MS (SPMS) is supported by its mechanism of action, which appears to be mediated, at least in part, through activation of the nuclear factor (erythroid derived 2)-related factor 2 (Nrf2). Nonclinical studies have shown DMF to have both cytoprotective and antiinflammatory effects. Studies in SPMS patients and pre-clinical models show that the active metabolite of DMF, monomethyl fumarate (MMF), penetrates the CNS; however, the effect of DMF on neuronal and glial CSF biomarkers is unknown.

**Objectives:** To explore the effect of DMF on neuronal and glial biomarkers in the CSF of SPMS patients.

**Methods:** Sixteen SPMS patients were treated with oral DMF 120 mg twice daily (BID) for 4 weeks, followed by oral DMF 240 mg BID for 24 weeks. CSF levels of neurofilament light (NfL), tau, glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCH-L1) were measured by the Single Molecule Array (SIMOA) assay at baseline, week 6 and week 28. CSF samples from four healthy controls were also analyzed.

**Results:** At baseline patients had a mean EDSS of 4.4, disease duration of 22.5 years, and no Gd<sup>+</sup> lesions. Baseline CSF NfL levels (mean±SD) in SPMS patients were 572±296 pg/mL and in healthy subjects 303±193 pg/mL. Mean EDSS decreased to 3.4, reflecting clinical improvement in 9 of 13 patients; NfL remained stable over the course of DMF treatment to week 28 (569±316 pg/mL), except for one patient who had disease exacerbation at week 18 when NfL levels increased to 1950 pg/mL and then decreased to 823 pg/mL by week 28. Levels of tau, GFAP and UCH-L1 remained stable over the 28 weeks.

**Conclusions:** In this small group of SPMS patients, baseline CSF NfL was relatively low, consistent with absence of Gd<sup>+</sup> lesions, remained stable during DMF treatment, and increased upon exacerbation in one patient. These data are consistent with the proposed value of NfL as a marker of MS disease activity and treatment monitoring.

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Natalia Penner: employee of and holds stock/stock options in Biogen.

### EP1601

#### Translational multi-omics identifies four peptides differentially regulated in the CSF of relapsing and progressive MS

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Biomarkers may predict the natural disease course in relapsing-remitting MS (RRMS), identify patients with need of early aggressive treatment, and may help in determining transition from RRMS to progressive disease early.

Here we used a translational multi-omics approach to identify potential biomarkers in the cerebrospinal fluid (CSF) of patients with RRMS, and secondary/primary progressive MS (SPMS/PPMS).

Demyelination was induced in mice by cuprizone (CPZ) administration for 4 weeks, while acute and full remyelination was induced by suspending CPZ for 2 and 14 days. The 4x44K Agilent Whole Mouse Genome Microarray detected 1239 differentially expressed genes in the de- and remyelinated corpus callosum. Comparison of these genes to the transcriptome of MS lesions identified 91 overlapping homologous genes and 7 susceptibility genes. By liquid chromatography mass spectrometry (LC-MS/MS), we detected 19 proteins of these 98 genes in pooled CSF of PPMS, RRMS and SPMS, respectively. We selected additional 32 out of the 98 genes based on biological function, and designed 132 peptides representing these 51 homologous proteins. In 97 individual CSF samples of 30 PPMS, 27 SPMS and 41 RRMS, we measured the levels of the 132 peptides by targeted proteomics, i.e. parallel reaction monitoring (PRM). Four proteins were differentially regulated among MS subgroups: tyrosine protein kinase receptor UFO (UFO-Axl), TIMP-1, apolipoprotein C-II (APOC2), and beta-2-microglobulin (B2M). Their genes were up-regulated during acute remyelination in the mouse brain. Immunohistochemistry indicated TIMP1

expression by oligodendrocyte precursor cells, while UFO-Axl and APOC2 by macrophages/microglia within demyelinating lesions. By using MesoScale, we correlated the concentration of 36 inflammatory molecules, neurofilament light chain (NF-L) and the 4 peptides in the CSF of 17 RRMS patients. The level of UFO-Axl and TIMP-1 negatively correlated with the concentration of IL-6; UFO-Axl also negatively correlated with concentration of MCP-1. B2M negatively correlated with the concentration of TARC. In contrast, APOC2 showed positive correlation with the concentration of IL-16, IL-2 and eotaxin-3.

This proof of concept study suggests that pathology-based translational multi-omics may identify potential biomarkers in MS.

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### Disclosure

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### EP1602

#### Disease modifying therapies alter microRNA expression patterns in distinct immune cell subsets in relapsing-remitting multiple sclerosis

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**Background:** MicroRNAs are small non-coding RNA molecules that regulate the expression of genes post-transcriptionally. In the context of MS, several microRNAs are dysregulated in both immune cells and plasma. Identifying altered microRNA expression patterns between MS patient prescribed various disease-modifying therapies (DMTs) may further elucidate the mechanism(s) of action for DMTs and assist in predicting an individual's immune and clinical response to a particular therapy.

**Objective:** The objective of this study was to identify whether DMTs influence the dysregulated microRNA expression that is observed in the immune cells (T cells, B cells and monocytes) of MS patients. Furthermore, microRNA expression in both plasma and specific immune cell subsets will be correlated with clinical disability.

**Methods:** Plasma and peripheral blood mononuclear cells were collected from age and sex-matched healthy controls and relapsing-remitting MS patients, including both treatment naïve and patients prescribed specific DMTs. Isolation of CD19+ B cells, CD14+ monocytes, CD8+ T cells and CD4+ T cells was

performed by magnetic-activated cell sorting. RNA was isolated from plasma and individual cell subsets. qPCR was used to quantify the expression of miR-223, -155, -146a, -146b, -19a and -365. Expression was correlated with EDSS.

**Results:** A significant decrease in miR-19a was observed in the plasma of MS patients vs healthy controls and was independent of treatment. Compared to healthy controls, analysis of CD14+ microRNA demonstrated increases in mir -146b, -223 and -365a in MS patients; teriflunomide normalized the expression of all microRNAs within the CD14+ population. In CD4+ and CD8+ T cells from RRMS patients, mir-155 was increased, however teriflunomide and dimethyl fumarate only normalized miR-155 expression within helper, but not cytotoxic, T cells. No significant differences were found between healthy control and MS patient B cells, however miR-223 was upregulated by treatment with DMF. No microRNAs were significantly correlated with EDSS.

**Conclusion:** Our results indicate that microRNAs are dysregulated in several immune cell subsets of RRMS patients and can be significantly altered by DMTs. Unique cellular microRNA expression patterns may therefore serve as potential disease biomarkers and/or elucidate further mechanism(s) of action.

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## EP1603

### Autoantibodies in neuromyelitis optica spectrum disorder and clinical characteristics

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**Background:** Multiple sclerosis with antinuclear antibody (ANA) has been reported to demonstrate more benign disease course than the disease without ANA. In neuromyelitis optica spectrum disorder (NMOSD), it is unclear whether autoantibodies including ANA are protective or toxic markers. We aimed to compare clinical characteristics and prognosis between NMOSD patients with and without ANA.

**Methods:** We reviewed the Asan Medical Center registry between January 2007 and June 2015 retrospectively, and analyzed data of patients who were diagnosed of seropositive NMOSD. Patients were classified into two groups according to the presence of ANA. The frequency of autoantibodies, annual relapse rates, spinal and orbital magnetic resonance imaging (MRI) findings during attacks were compared between the groups. The presence of poor functional outcome, defined by Expanded Disability Status Scale score  $\geq 6$  or visual acuity  $\leq 0.1$ , was also compared. For the MRI findings, numbers of vertebral segments and optic nerve segments (retrobulbar/canicular/intracranial/optic chiasm/tract) involved during attacks were investigated for myelitis and optic neuritis, respectively.

**Results:** A total of 63 patients with NMOSD was identified, and the median follow-up duration from the disease onset was 7 (IQR 3–11) years. Of them, 26 patients had ANA in their disease courses. The ANA-positive group demonstrated more frequent autoantibodies such as SSA/Ro, SSB/La, and double stranded DNA antibody. Clinically, however, between the ANA-negative and ANA-positive groups, annual relapse rates (median [IQR], 0.6 [0.4–1] vs. 0.5 [0.3–0.8],  $p=0.321$ ) and average lesion extents of myelitis (vertebral segments: 8 [5–12] vs. 7 [4–12],  $p=0.421$ ) and of optic neuritis (optic nerve segments: 2 [1–3] vs. 2 [1–2],  $p=0.477$ ) on MRI during attacks were comparable. The presence of poor functional outcome (17 [45.9%] in the ANA-negative group vs. 13 [50.0%] in the ANA-positive group) also did not differ.

**Conclusions:** In our NMOSD cohorts, patients with ANA showed more frequent autoantibodies than those without. However, these autoantibodies were not associated with benign or malignant disease characteristics. Autoantibodies other than aquaporin-4 antibody are commonly observed, but may be a bystander in NMOSD patients.

## Disclosure

Nothing to disclose

## EP1604

### The role of metabolomics in multiple sclerosis sub-classification and clinical course

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Elucidating potential biomarkers in autoimmune neuroinflammatory diseases, is important to identify disease specific metabolic signatures. This is particularly relevant to complex diseases such as Multiple Sclerosis (MS). Studying specific metabolomic pathways in MS patients provide valuable clinical information to monitor the disease progression and guide therapeutic decisions. The authors attempted to quantify low molecular weight potential biomarkers for MS progress monitoring, by developing and validating a novel fast and sensitive analytical method in patients' serum.

Pre-treatment sera were obtained from 30 Relapse Remit MS patients (RRMS) (18 females-12 males) during a clinical relapse. Serum samples were also collected from 20 patients with Clinical Isolated syndrome (CIS) (11 females-9 males) and 20 healthy individuals (13 females-7 males) matched for age and gender. Disease duration, relapse rate (rr for RRMS group), number of Gadolinium enhanced lesions (GdE+) and EDSS score were recorded for each MS patient.

High performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) was applied for the simultaneous



detection and quantification of the following suspected biomarkers: Choline, Acetyl-choline, Histidine, Histamine, Imidazoleacetic acid, Arginine, Citrulline and 3-Nitro-Tyrosine.

Acetyl-choline (Ach) was not detected in CIS and RRMS groups (Limit of Detection, LOD: 100pg/ml) while Choline was significantly reduced in RRMS and CIS groups ( $F(2,67)=11,392$ ,  $p=0.001$ ). Histamine was not detected in RRMS group (LOD: 1ng/ml) while Imidazoleacetic acid was quantified in all groups (Limit of Quantification, LOQ: 500pg/ml). Citrulline was significantly elevated in the RRMS group ( $F(2,67)=5.811$ ,  $p=0.005$ ) and 3-nitrotyrosine (product of  $\text{NO}_x$ ) was detected in RRMS group only (LOQ: 10ng/ml). In addition, Citrulline was correlated with rr, EDSS score and GdE+ lesions in RRMS participants ( $r=0.620$ ,  $p=0.001$   $r=0.447$ ,  $p=0.05$   $r=0.599$ ,  $p=0.001$ ) and Histidine was correlated with EDSS only ( $r=0.620$ ,  $p=0.001$ ).

Our results highlight the importance of the correlation of specific metabolomic signatures with certain clinical MS profiles, as it can provide valuable information regarding the progress of the disease. This is a preliminary report of an ongoing research project regarding the screening and quantification of potential MS biomarkers.

## Disclosure

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Tsivgoulis G.: nothing to disclose

Papageorgiou Ch.: nothing to disclose

Thomaidis N.: nothing to disclose

Voumavourakis K.I.: nothing to disclose

## EP1605

### NFL and CXCL13 reveal disease activity in clinically and neuro-radiologically stable MS

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**Background:** Increased levels of Neurofilament light protein (NFL) in cerebrospinal fluid (CSF) indicate axonal degeneration and are associated with disease activity in MS. The concentration of CSF-CXCL13 has strong association with neuroinflammation and B-cell infiltration. In MS, CSF-CXCL13 levels correlate to CSF-NFL levels, supporting a connection between inflammation and axonal injury in the pathogenesis of MS.

**Objective:** To investigate the degree of inflammation and axonal injury in patients of different MS phenotypes MS by comparing the changes in the CSF levels of NFL and CXCL13 in patients with relapsing-remitting (RRMS) and progressive multiple sclerosis (PrMS) during disease activity and during disease modifying treatments (DMTs).

**Methods:** We included 202 RRMS and 84 PrMS patients, of those 95 RRMS and 47 PrMS were followed for 12 months. CXCL13

and NFL were determined by ELISA. Disease activity was defined as a relapse within 3 months prior to sampling and/or one or more gadolinium (Gd) contrast enhancing lesions on MRI. The increased levels of NFL and CXCL13 were defined as levels above the following reference values: CSF-NFL reference range for different ages are < 30 years: < 380ng/L; 30-40 years: < 560 ng / L; 40 years- < 60 years: < 890 ng / L; > = 60 years: < 1850 ng / L. CSF-CXCL13 reference value is > 7.8 ng / L.

**Results:** In RRMS and PrMS with disease activity, NFL levels were increased in 63.6% and 64.5%, and CXCL13 levels were increased in 53.3% and 58.1%, and both were increased in 34.1% and 45.2%, respectively. In RRMS and PrMS without disease activity, NFL levels were increased in 34.1% and 34.7%, and CXCL13 levels were increased in 14.1% and 17%, and both were increased in 8% and 11.9%, respectively. In 4.5% RRMS and 9.1% PrMS with low CSF levels of NFL and CXCL13 had signs of ongoing disease activity.

The treatment with various DMTs decreased the levels of NFL and CXCL13 in 78% RRMS ( $p < 0.001$  and  $p < 0.001$ ) and in 64% PrMS ( $p=0.014$  and  $p=0.063$ ), respectively.

**Discussion:** The increased CSF levels of NFL and CXCL13 in MS patients without a recent relapse and without contrast enhancing lesions on MRI indicate a residual disease activity not detected clinically or by MRI. Further, DMTs reduced NFL and CXCL13 levels supporting treatment effects on both inflammation and degeneration. Thus, CSF biomarkers add information that might facilitate the monitoring of disease activity and therapeutic decision in MS patients.

## Disclosure

LN has no disclosures.

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CM has received honoraria for lectures and advisory boards from Biogen and Novartis.

AS has served on advisory board for Sanofi-Genzyme and has received travel funding from Biogen Idec.

KB has served as a consultant or at advisory boards for Alzheon, Eli-Lilly, Fujirebio Europe, IBL International and Roche Diagnostics, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg.

JL has received travel support and/or lecture honoraria from Biogen, Novartis, Teva and Genzyme/SanofiAventis; has served on scientific advisory boards for Almirall, Teva, Biogen, Novartis and Genzyme/SanofiAventis; serves on the editorial board of the Acta Neurologica Scandinavica; has received unconditional research grants from Biogen, Novartis and Teva.

## EP1607

### A comprehensive *in silico* analysis of transcripts upregulated in multiple sclerosis patients and ZIKV infection: identification of similar pathways

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Increasing reports link recent ZIKV infections to various forms of neuropathology, including microcephaly and Guillain-Barré syndrome (GBS). The pathogenesis viral infections and the development of autoimmune diseases may have viral trigger and are linked to disturbances in immune response. Here we compared upregulated transcript profile of multiple sclerosis (MS) patients and infection by ZIKV (human neural progenitor cells, human maternal decidual tissues and human fetal brain neural stem cells, all exposed to ZIKV) using bioinformatics tools. In lists available in online databases, we found a total of 593 genes upregulated in MS and 534 in ZIKV infection, 36 genes were shared between them. To further understand the impact of MS and ZIKV infections on the biological processes, we used Gene ontology (GO). Several biological processes were similarly significantly enriched for both MS and ZIKV transcriptomes, these terms include mainly the cell proliferation, response to stress and immune response. In comparative analyses of protein-protein interactions (PPI) network design we observed network with 289-261 nodes and 878-778 connectors in ZIKV and MS network, respectively. Centrality parameters (Node degree and Betweenness) of each node were analyzed. These pathways obtained statistical significance ( $p < 0.05$ ). *STAT1*, *ISG15*, *HERC5*, *OAS1*, *IFIT3*, *IRF7*, *IFIT1*, *MX1*, *IFI35* and *IFIT2* were the 10 top hub genes in ZIKV network. In MS network, *JUN* was the gene capable of making the largest numbers of connections with other genes and joining several sub-networks, thus being considered the hub-bottleneck, which controls the most of the information of a network. The 10 top hub in this network were *JUN*, *CDC20*, *FOS*, *TOP2A*, *AURKB*, *KIF2C*, *RRM2*, *CREBBP*, *IL8* and *CDC45*. We also did an analysis of the two networks together to identify molecular signatures similar in MS and ZIKV infection. The main functional enrichment categories in this analysis were regulation of apoptosis, chemotaxis, regulation of JAK-STAT cascade, immune response, positive regulation of cell proliferation and signal transmission. The approaches employed in this study enabled us to report sets of genes that according to their physical interactions are predicted to be molecular signatures similar in MS and ZIKV infection, improving the understanding of this new outbreak and, in the future, may support a new proposal of prognostic and treatments.

## Disclosure

The authors declare that they have no competing interests.

## EP1608

### CSF interleukin 6 concentrations in pseudotumoral inflammatory CNS lesions suspicious of CNS lymphoma

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**Background:** Interleukin (IL)-6 is a cytokine with a wide range of biological functions. Its upregulation in the cerebrospinal fluid (CSF) is considered as a marker of central nervous system (CNS) inflammation.

**Objective:** Our aim was to analyse the diagnostic significance of CSF IL-6 levels among various CNS pseudotumoral inflammatory lesions (PIL) and primary CNS lymphoma (PCNSL).

**Methods:** We retrospectively analysed the CSF IL-6 concentration in 43 patients admitted for suspected primary CNS lymphoma between February 2014 and March 2017. 28 patients were positively diagnosed with PCNSL, 15 with various inflammatory CNS disorders. We correlated the results with CSF IL-10, a recently established diagnostic biomarker of PCNSL.

IL concentrations were measured by FCM using the cytometric bead array (CBA) technique (BD Biosciences) with a detection limit set at 2.5 pg/ml.

**Results:** In the PCNSL group, the median CSF IL-6 concentration with interquartile range (IQR) was 8 pg/ml IQR (5 - 18.5). For the patients with other PIL the median concentration was of 70 pg/ml, IQR (5 - 1368). A group comparison showed significantly higher CSF IL-6 levels in patients with PIL compared to PCNSL ( $p=0.032$ ). Moreover, IL-6 was correlated with CSF cell count for the whole cohort ( $r=0.45$ ,  $p=0.002$ ), as well as for the PIL group ( $r=0.56$ ,  $p=0.028$ ), but not in PCNSL group ( $r=0.3$ ,  $p=0.13$ ). There was no correlation between CSF IL-6 in the two groups ( $r=0.023$ ,  $p=0.9$ ). Moreover, we found significantly higher CSF IL-10 levels in patients with PCNSL compared to the group with PIL ( $p<0.001$ ).

**Conclusion:** Our study suggests that CSF IL-6 levels could represent, in addition to CSF IL-10, a useful biomarker in the diagnosis of CNS PIL that may mimic PCNSL.

## Disclosure

Nothing to disclose

## EP1609

### Ozanimod (RPC1063) reduces the plasma biomarker neurofilament light chain in preclinical rodent models of multiple sclerosis

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Receptos, a wholly owned subsidiary of Celgene, San Diego, CA, United States

**Background:** Ozanimod (RPC1063) selectively targets S1P<sub>1R</sub> and S1P<sub>5R</sub> and has shown therapeutic benefit in clinical trials of relapsing multiple sclerosis (RMS). S1P<sub>1R</sub> and S1P<sub>5R</sub> expression on T and B cells as well as glial cells provides a series of critical control points by which ozanimod can disrupt the inflammatory cascade of MS. Furthermore, ozanimod penetrates the blood-brain barrier and potentially promotes CNS-tissue preservation. Neurofilament light chain (NfL) is released into the cerebrospinal fluid and serum/plasma following axonal injury and degeneration. It may serve as a biomarker for monitoring neurological damage in RMS.

**Methods:** The concentration of NfL was measured in the plasma of experimental autoimmune encephalomyelitis (EAE) and cuprizone-induced demyelination mouse models. Blood was isolated

from mice via terminal cardiac puncture and plasma NfL was measured at Quanterix (Lexington, MA) using the Simoa technology platform. In EAE, mice were therapeutically dosed with ozanimod for 14 days and then spinal cords were assessed for inflammation by H&E staining and demyelination by Luxol Fast Blue at termination. In the cuprizone model, mice were treated with an ozanimod surrogate (RP-101074) for six weeks concurrently with cuprizone and corpus callosum sections at termination were stained with SMI-32 to evaluate neuronal breaks.

**Results:** Plasma NfL was significantly elevated in EAE and cuprizone-treated mice over naïve controls. Elevated plasma NfL levels correlated with spinal cord inflammation and demyelination in EAE and with neuronal breaks in the corpus callosum of mice treated with cuprizone. Ozanimod treatment in EAE significantly reduced plasma NfL levels correlating with a significant reduction in clinical scores and spinal cord inflammation and demyelination. Mice treated with RP-101074 in the cuprizone model had significantly reduced plasma NfL and neuronal breaks, supportive of a neuroprotective effect.

**Conclusion:** Plasma NfL was significantly elevated in EAE mice and in the cuprizone-treated mice compared to naïve, non-diseased induced animals. Elevated plasma NfL correlated with clinical scores and spinal cord inflammation and demyelination in EAE as well as with neuronal breaks in the cuprizone model. In both of these preclinical studies, plasma NfL served as a biomarker indicative of CNS injury, inflammation and demyelination. These observed effects indicate a potential positive and direct CNS effect of ozanimod.

## Disclosure

K. R. Taylor Meadows, Shareholder: Celgene.  
F. L. Scott, Shareholder: Celgene.  
C. Villescaz, Shareholder: Celgene.  
B. Clemons, Shareholder: Celgene.  
C. Lopez, Shareholder: Celgene.  
S. Sawa-Ballweber, Shareholder: Celgene.  
K. Dines, Shareholder: Celgene.  
G. J. Opitck, Shareholder: Celgene.

## EP1610

### JCPyV microRNA in plasma inversely correlates with JCPyV seropositivity among long-term natalizumab-treated relapsing-remitting multiple sclerosis patients

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**Background:** Sensitive biomarkers are needed to better detect or evaluate the multiple sclerosis (MS) patients for natalizumab (NTZ)-associated risk of progressive multifocal leukoencephalopathy (PML). Currently used risk stratification algorithm, mainly based on JC polyomavirus (JCPyV) serology, has not led to a reduction of PML incidence. JCPyV encoded microRNAs (miRNAs) could serve as sensitive biomarkers for PML risk because these miRNAs are frequently detected in plasma, urine

and CSF of immunosuppressed and healthy individuals, both JCPyV seropositive and seronegative.

**Objective:** To evaluate the presence and prevalence of JCPyV miRNAs in plasma of NTZ-treated MS patients, and to explore their biomarker potential for NTZ-associated PML risk assessment.

**Methods:** Altogether 102 plasma samples from 49 NTZ-treated and 28 interferon-beta (IFN- $\beta$ )-treated relapsing-remitting MS patients, and 25 healthy controls (HCs) were analysed for jcv-miR-J1-5p (5p miRNA) and jcv-miR-J1-3p (3p miRNA) expression.

**Results:** The overall detection rate of 5p miRNA was 80.5 % (62/77) among MS patients and 92% (23/25) in HCs. When the patients were grouped based on current medication, the overall detection rate for 5p miRNA was 84% (41/49) among NTZ-treated patients, and 75% (21/28) among IFN- $\beta$ -treated patients. However, the differences in detection rates were not statistically significant ( $p>0.5$ ). Further, in groups based on the presence of JCPyV antibodies, 5p miRNA detection rates were similar among JCPyV seropositive and seronegative patients. Relative 5p miRNA expression levels were lower in NTZ-treated patients as compared to patients treated with IFN- $\beta$  ( $p=0.027$ ) but not to HCs. Moreover, 5p miRNA expression inversely correlated with anti-JCPyV antibody index among JCPyV seropositive long-term NTZ-treated patients ( $r=-0.756$ ;  $p=0.002$ ). The overall detection rate of 3p miRNA was low.

**Conclusion:** Our results suggest that JCPyV miRNA in plasma may be linked to the reactivation of persistent JCPyV, enhanced virus replication, and eventually to the risk of developing PML among NTZ-treated MS patients. However, further study is warranted in a larger data set including samples from PML patients to confirm the clinical relevance of JCPyV miRNA as a sign of/in viral reactivation, and to identify its potential to predict developing PML risk.

## Disclosure

The authors have no conflict of interests to declare.

## EP1611

### Comparing the CSF proteome of neuromyelitis optica patients with and without anti-AQP4 antibodies - preliminary data

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**Background:** Neuromyelitis optica (NMO) is an inflammatory and demyelinating auto-immune disease of the central nervous system. Subgroups of NMO patients have been identified, including anti-AQP4 seropositive and anti-AQP4 seronegative patients. We aim to gain insight in the pathophysiology of NMO, in patients with and without anti-AQP4 antibodies, using CSF proteomic analysis.

**Methods:** CSF was enzymatically digested and analysed by high resolution mass spectrometry (Orbitrap QX+) after separation using a 90 minute LC gradient on a C18 column. The resulting



spectra were analysed using specialized software (Progenesis LC-MS) and differentially abundant proteins between the groups were identified. Subsequently the differentially abundant proteins were submitted to Ingenuity Pathway Analysis (IPA) for assessment of their connection and roles in biological pathways that might be relevant to disease pathology.

**Results:** CSF of 12 anti-AQP4 positive NMO patients and 16 anti-AQP4 negative patients were available and analysed. The anti-AQP4 group consisted of more females (75% vs 52%) and were older at onset (median 46 years vs median 38 years). In total, we identified 6595 peptides belonging to 725 proteins, with a peptide false discovery rate (FDR) of 0.02% and a protein FDR of 0.8%. These proteins were analysed with stringent criteria to detect the significantly differentially abundant proteins between the groups. Six proteins were significantly higher in abundance in the AQP4-ab positive patients than in the AQP4-ab negative patients. These proteins are involved in biological processes, including neurogenesis, synaptogenesis, cell adhesion properties and cell proliferation.

**Conclusion:** This preliminary data shows that the CSF proteome of anti-AQP4 positive patients has higher abundance for six proteins involving in neuro-regenerative processes. Further analyses are needed to confirm these findings.

## Disclosure

Yu Yi Wong: nothing to disclose

Marcel Stoop: nothing to disclose

Roos van der Vuurst de Vries: nothing to disclose

Christoph Stingl: nothing to disclose

Theo Luiders: nothing to disclose

Bernard Hemmer: has served on scientific advisory boards for F. Hoffmann-La Roche Ltd, Novartis, Bayer AG, and Genentech; he has served as DMSC member for AllergyCare; he or his institution have received speaker honoraria from Biogen Idec, Teva Neuroscience, Merck Serono, Medimmune, Novartis, Desitin, and F. Hoffmann-La Roche Ltd; his institution has received research support from Chugai Pharmaceuticals and Hoffmann-La-Roche; holds part of two patents; one for the detection of antibodies and T cells against KIR4.1 in a subpopulation of MS patients and one for genetic determinants of neutralizing antibodies to interferon  $\beta$ .

Rogier Hintzen: Received honoraria for serving on advisory boards for Biogen Idec, Roche, Sanofi. He participated in trials with BiogenIdec, Merck-Serono, Roche, Genzyme and Novartis

## EP1612

### OFSEP biobank: high quality samples for powerful research on MS biomarkers

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The Observatoire Français de la Sclérose En Plaques (OFSEP) is a French national cohort of patients with multiple sclerosis (MS),

granted in 2011 for a ten-year tenure by the French National Research Agency. The OFSEP's biobank aims to provide research high quality biological samples from MS patients, associated to clinical data.

Selected groups of patients only are currently sampled: Clinical Isolated Syndromes (CIS), Radiologically Isolated Syndromes (RIS), primary progressive MS (PPMS), NeuroMyelitis Optica Spectrum Disorders (NMOSD), Acute Disseminated EncephaloMyelitis (ADEM) and multifocal leukoencephalopathy (PML). Blood and urine collection are mandatory, CSF and stool are optional.

To achieve high quality samples, OFSEP relies on 13 French biobanks certified with the NF S96-900 norm.

Samples of serum, plasma, DNA, PBMC (Peripheral Blood Mononuclear Cells), urine, CSF, CSF cells and stool are conditioned in sterile conditions and rapidly stored in a highly secured manner. According with international recommendations, delay between sampling and freezing is less than 4h (24h for PBMC).

More than 15 000 biological samples are now available for MS research, corresponding to 241 CIS patients, 36 RIS patients, 108 PPMS patients, 148 NMOSD patients, 11 patients with ADEM and 4 PML. Diagnosis and respect of inclusion criteria were controlled by using EDMUS clinical data and when necessary by expert groups (RIS and NMOSD).

OFSEP's biobank associated with clinical data from EDMUS software provides the opportunity to achieve high level research on MS biomarkers. Biological samples and associated data are open to academic and industrial research. In a near future, collection will extend to relapsing-remitting and atypical forms of MS.

## Disclosure

Nathalie Dufay, Romain Casey, Benjamin Britsch-Fayet, Sylvain Lehman, Géraldine Gallot, Patrick Gelé, Bertrand Fontaine, Eric Thouvenot, Romain Marignier, Hélène Zephir and David Laplaud: nothing to disclose

## EP1613

### Serum Neurofilament light chain as a predictor of long-term outcomes in patients with CIS in the BENEFIT 11 trial

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**Background:** Serum Neurofilament light chain (sNfL) is a promising biomarker of neuro-axonal injury. Recent studies have shown associations with clinical and MRI disease activity and significant predictive value for relapses and worsening of disability. Follow up from patients with clinically isolated syndrome (CIS) who were enrolled in BENEFIT and had comprehensive assessments after 2, 5 and 11 years provides an opportunity to study the short- and long-term predictive value of sNfL.

**Objective:** To analyse the predictive capacity of baseline and year 1 sNfL measurements for outcomes at 2, 5 and 11 years. Further, to investigate associations between clinical and imaging variables and sNfL levels measured at baseline, 1 and 11 years.

**Methods:** Patients with CIS within 60 days were randomized to initial treatment with interferon beta-1b or placebo for 2 years or until diagnosis of clinically definite MS (CDMS). After conversion to CDMS or 2 years, patients on placebo could switch to interferon beta-1b or another treatment. Prospective follow up rater-blinded to initial randomization continued to year 5. Eleven years after randomization, patients were asked to participate in a comprehensive re-evaluation including clinical, imaging and blood laboratory tests. sNfL was measured by Single Molecule Array (Simoa) assay. The relation of sNfL to relapse-, disability- and MRI related endpoints at Years 2, 5 and 11 is investigated by uni- and multivariate regression analyses. Baseline covariates include sex; age; lowest EDSS up to Month 6 visit; mono/multifocal onset; presence of optic nerve, brainstem, or spinal cord lesions; PASAT3; Timed 25-Foot Walk and 9-Hole Peg test scores; number and volume of hypointense T1, gadolinium-enhancing T1, and T2 lesions; cerebral volume; and initial treatment assignment.

**Results:** sNfL was measured in 1018 samples (BL n=463; year 1, n=330, and year 11, n=225). Results of uni- and multivariate analyses will be presented.

**Conclusions:** Using the Simoa technology that allows highly sensitive and robust quantitation of sNfL levels our study will provide insights into the predictive value of sNfL for mid and long-term outcomes in patients with a first clinical inflammatory demyelinating event.

## Disclosure

Study supported by Swiss National Research foundation and Bayer

J Kuhle's institution (University Hospital Basel) received and used exclusively for research support: consulting fees from Biogen, Novartis, Protagen AG, Roche, Teva; speaker fees from the Swiss MS Society, Biogen, Novartis, Roche, Genzyme; travel expenses from Merck Serono, Novartis, Roche; grants from ECTRIMS Research Fellowship Programme, University of Basel, Swiss MS Society, Swiss National Research Foundation (320030\_160221), Bayer AG, Biogen, Genzyme, Merck, Novartis, Roche.

C Barro has received travel support from Teva and Novartis.

G Edan has received honoraria for lectures or consulting from Biogen Idec, Merck Serono, and Sanofi-Aventis, and received personal compensation for serving on the BENEFIT scientific advisory board and for speaking from Bayer AG. He has also received research support from Serono, (a grant to University Hospital to support a research program on MRI in MS) and from Teva (a grant to support a research program on anti-IBF neutralizing antibodies).

MS Freedman has received compensation from Bayer HealthCare, Biogen Idec, EMD Canada, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, and Teva Canada Innovation for consulting services. He also participates in a Genzyme-sponsored speakers bureau.

H-P Hartung has received honoraria for consulting and speaking at symposia from Bayer AG, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Teva, and Sanofi-Aventis, with approval by the rector of Heinrich-Heine University.

X Montalbán has received speaking honoraria and travel expenses for scientific meetings and has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Bayer, Biogen Idec, EMD, Genentech, Genzyme, Merck Serono, Neurotec, Novartis, Sanofi-Aventis, Teva Pharmaceuticals, and Almirall.

F Barkhof has received compensation for consultancy from Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, Genzyme, Roche, and Teva, and has received research support from the Dutch Foundation for MS research (an NGO).

EJ Fox has received consulting fees, honoraria, travel, or research support from Acorda, Bayer, Biogen Idec, Eli Lilly, EMD Serono, Genzyme, GlaxoSmithKline, Novartis, Ono, Opexa Therapeutics, Pfizer, Roche, Sanofi, and Teva.

B Hemmer has served on scientific advisory boards for Roche, Novartis, Bayer Schering, and Genentech; has received speaker honoraria from Biogen Idec and Roche; and has received research support from Chugai Pharmaceuticals. He holds part of a patent for the detection of antibodies and T cells against KIR4.1 in a subpopulation of patients with MS and genetic determinants of neutralizing antibodies to interferon-beta.

S Schippling has received research grants from Biogen, Bayer Healthcare, Novartis and Sanofi Genzyme, and consulting/speaker fees as well as travel support from Bayer Healthcare, Biogen, Merck Serono, Novartis, Teva, and Sanofi-Genzyme.

R Koelbach is a salaried employee of PAREXEL International.

EM Wicklein is a salaried employee of Bayer AG.

L Kappos' institution (University Hospital Basel) received in the last 3 years and used exclusively for research support: steering committee/consulting fees from Actelion, Addex, Bayer HealthCare, Biogen, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono, Pfizer, Receptos, Sanofi-Aventis, Santhera, Siemens, Teva, UCB, and Xenoport; speaker fees from Bayer HealthCare, Biogen, Merck, Novartis, Sanofi-Aventis, and Teva; support of educational activities from Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi-Aventis, and Teva; royalties from Neurostatus Systems GmbH; grants from Bayer HealthCare, Biogen, the European Union, Merck, Novartis, Roche, Roche Research Foundations, the Swiss Multiple Sclerosis Society, and the Swiss National Research Foundation.

## EP1614

**mTOR signaling plays a crucial role in IFN- $\beta$  non-responsiveness in MS patients with high serum Sema4A levels**

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**Background:** Interferon-beta (IFN- $\beta$ ) is one of the first-line therapies in relapsing-remitting multiple sclerosis (RRMS) and one-third of patients are poor responders to this therapy. We previously reported that a class IV semaphorin (Sema4A) is increased in the sera of MS patients, those with high Sema4A do not respond well to IFN- $\beta$  therapy. Although Correlation between Sema4A and Mammalian target of rapamycin (mTOR) signaling in CD8+ T cells has been shown recently, the relationship in CD4+ T cells has not been unknown.

**Goals:** In this study, we confirmed reproducibility of our previous study in larger cohort and evaluate new outcome measure of MS. In addition, we tried to reveal the mechanism by which Sema4A inhibits the therapeutic effect of IFN- $\beta$ .

**Methods:** This study examined 201 RRMS patients (58 facilities in Japan) who met the MacDonald criteria 2010. Serum Sema4A levels were examined using sandwich ELISA. We also evaluated clinical severity of 48 RRMS patients receiving IFN- $\beta$  therapy. To analyze the effect of Sema4A in CD4+ T cell differentiation, we stimulated coculture of human CD4+ and CD14+ cells with recombinant Sema4A.

**Results:** MS patients with high serum Sema4A tended to have earlier age of onset, higher annual relapse ratio, and more severe EDSS score change than those with low Sema4A. No significant differences were found in positive ratio of oligoclonal immunoglobulin G bands and distribution of brain MRI lesions. A total of 9 of 28 (32.1%) patients with low Sema4A achieved remission status after 5 years from start IFN- $\beta$  therapy, but only 1 of 12 (8.3%) patients with high Sema4A did. When we differentiated human CD4+ T cells, Sema4A promoted phosphorylation of mTOR (Ser2448) and ribosomal protein S6 kinase beta-1 (S6K1) which acts downstream of mTORC1 pathway. Moreover, Sema4A increased the proportion of both Th1 and Th17 cells, which was canceled by rapamycin, mTOR inhibitor.

**Conclusion:** Our results suggest that high serum Sema4A correlates with IFN- $\beta$  resistance in RRMS patients by activation of mTOR signaling.

## Disclosure

Akiko Hosokawa Namba: nothing to disclose  
Tatsusada Okuno: nothing to disclose  
Toru Koda: nothing to disclose  
Kazuya Yamashita: nothing to disclose  
Mikito Shimizu: nothing to disclose  
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## EP1615

### Intrathecal IgM synthesis is associated with conversion of CIS patients to definite MS

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**Background:** Detection of intrathecal immunoglobulin G (IgG) synthesis indicated by oligoclonal bands (OCBs) or in the Reiber diagram are well established markers for acute and chronic inflammation in the central nervous system (CNS). Especially OCBs are connected to a more severe disease course in multiple sclerosis (MS). In the last years also IgM OCBs gained impact and were associated with a worse clinical outcome if present, particularly in the progressive forms of MS. However, the detection of IgM OCBs is challenging and conformation of those findings by several independent groups is still pending. In this study we compared the predictive values of IgG OCBs, intrathecal IgG and IgM production towards conversion of CIS patients to definite MS.

**Methods:** We retrospectively collected data of IgG OCBs, intrathecal IgG and IgM production as indicated by the Reiber diagram of CIS patients who attended university hospital of Ulm during their very first relapse as well as clinical data such as extended disability status scale (EDSS) and time to conversion to MS (CTM) in months.

**Results:** 50 patients were included of whom 60 % were female and the median age was 34 (IQR 23-45). The median follow up time was 35 months (IQR 24-46), whereas in this time 48 % converted to clinical definite MS. 80 % of the patients showed a positive OCB finding, 28 % an intrathecal IgG and 18 % an intrathecal IgM production.

There was no correlation of the numerical quotients for IgG and IgM to EDSS ( $p = 0.43$  and  $0.37$ , respectively) but EDSS levels were significantly higher in IgG OCB positive compared to OCB negative patients ( $p = 0.016$ ).

The hazard ratio for conversion was highest for patients showing an intrathecal IgM production (HR 2.5 compared to 2.1 for intrathecal IgG production and 2.0 for OCB positivity). Furthermore, 89 % (8 of 9) patients with an intrathecal IgM production did convert to a definite MS, whereas the conversion prevalence for OCB positive subjects was 64 % and 75 % for patients with an intrathecal IgG production according to the Reiber diagram.

**Discussion:** Our data suggest that an intrathecal IgM production indicated by the Reiber diagram is a more specific risk marker for conversion than e.g. OCBs, nevertheless OCBs are still superior concerning sensitivity and are related with a higher EDSS in our study. This finding has to be confirmed by a larger study and should also be compared to IgM OCBs to see whether those two findings are comparable or independent of each other.

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## EP1616

**Determination of the altered metabolome as an expected biomarker of active plaques in relapsing-remitting multiple sclerosis patients**

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**Background:** Despite the establishment of some well-known factors involved in MS pathology, no specific biomarker of the disease is currently available. The cerebrospinal fluid (CSF) metabolome, defined as the set of all CSF metabolites might be important for MS diagnosis and management.

**Goals:** To assess differences in the CSF metabolite profiles between relapsing-remitting MS patients (RRMS) and healthy controls (HCs) according to the presence of active inflammatory plaques in the brain or cervical spinal cord on magnetic resonance imaging (MRI).

**Methods:** 14 RRMS patients and 12 HCs were included in the study. Patients were divided into 2 groups: MS-I group: 6 patients without disease modifying therapy (DMT) who showed active inflammatory plaques in the brain or cervical spinal cord on MRI and 8 MS patients lacking such plaques on MRI (MS-II group). To evaluate metabolome of CSF, <sup>1</sup>H NMR spectroscopy was used. The comparison of metabolic profile between MS-I, MS-II and HCs was conducted and the pathway analysis was performed.

**Results:** The CSF metabolome did not significantly differ between MS patients and HCs ( $R^2Y=0.09$ ,  $Q^2Y=-0.17$  - single-component score; permutation test statistic for separation distance:  $p=0.46$ ). The results of partial least square discriminant analysis (PLS-DA) indicated significant discrimination between the MS-I group and the MS-II group ( $R^2Y=0.70$ ,  $Q^2Y=0.56$  - single-component model; permutation test statistic for separation distance:  $p=0.024$ ). The variables predominantly responsible for the distinction between the MS-I and MS-II groups were spectral regions corresponding to lactate, creatine, L-glutamine, acetic acid, and D-glucose which revealed that concentrations of the identified metabolites were used to perform enrichment analysis that revealed that changes in CSF metabolite profiles in MS patients with active plaques on MRI primarily affected the pyruvate metabolism pathway.

**Conclusions:** Distinct metabolite profiles between RRMS patients with and without active inflammatory plaques in the brain or cervical spinal cord on MRI was found. The CSF metabolome was comparable between healthy individuals and MS patients which suggests that the metabolite profile is altered only during active MS processes. <sup>1</sup>H NMR spectroscopy is an analytical tool for metabolome determination and seems to be helpful in MS biomarker estimation.

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**Immunomodulation/  
Immunosuppression**

## EP1617

**Towards personalized dosing of natalizumab in multiple sclerosis: an ongoing multicentre trial in the Netherlands**

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**Background:** Natalizumab is an efficacious drug in the treatment of relapsing-remitting multiple sclerosis (RRMS). Despite the knowledge of a large variation in pharmacokinetics and patient characteristics, every patient receives the same treatment regimen of 300mg intravenously administered natalizumab every four weeks. We believe that a natalizumab concentration based treatment schedule may result in fewer hospital visits and lower costs, without decreasing drug efficacy.

**Objective:** To prove that extending dose intervals guided by serum concentrations of natalizumab will not result in radiological and clinical disease activity in completely stable RRMS patients treated with natalizumab.

**Study design:** A prospective multicentre, single arm trial.

**Study population:** Adult patients with RRMS with no evident disease activity during the last 12 months of natalizumab infusions with a minimum treatment duration of 12 months. Only patients with natalizumab trough concentrations of  $\geq 15\mu\text{g/ml}$  can enter the study.

**Intervention:** Before subsequent natalizumab infusions, serum natalizumab concentrations will be evaluated. If the concentration exceeds  $15\mu\text{g/ml}$  the dose interval will be extended with one week to a maximum of eight weeks. If serum concentration falls between  $10-15\mu\text{g/ml}$  patients will remain on their current schedule. If serum concentration drops below  $10\mu\text{g/ml}$  the infusion schedule will be put back with one week with a minimum of a four week interval. Patients will undergo 3 monthly brain MRI's with gadolinium and 3 monthly neurological testing, i.e. expanded disability status scale (EDSS). Furthermore, at baseline and at 12 months, patients will complete questionnaires including Short form-36 and Multiple Sclerosis Impact Scale-29.

**Main study parameters/endpoints:** The primary endpoint is the number of patients developing gadolinium enhancing lesions on brain MRI. Secondary endpoints are new or enlarging T2 lesions on brain MRI, clinical relapses, progression on EDSS and changes of subjective health measured with the questionnaires.

**Preliminary trial results:** The first patient was included in November 2016. So far, 30 patients have been included and  $>50\%$

of patients are treated with an interval  $\geq 6$  weeks. MRI follow-up showed no gadolinium enhancing lesions in included patients. Furthermore, no new/enlarging T2 lesions were found at MRI follow-up and no patient experienced a clinical relapse so far.

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E.L.J. Hoogervorst has received speaker and consulting fees from Merck-Serono, Biogen, TEVA, Genzyme and Novartis.

R.Q. Hintzen received honoraria for serving on advisory boards for Biogen Idec, Roche and Sanofi. He participated in trials with Biogen Idec, Merck-Serono, Roche, Genzyme and Novartis.

H.C. Weinstein has nothing to disclose.

M.P. Wattjes has received speaking and consultancy fees from Genzyme, Biogen, Novartis, Roche.

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### EP1618

#### Two-year follow-up of 19 patients treated with alemtuzumab for active relapsing-remitting MS: the Lyon's experience

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**Background:** Alemtuzumab has been approved by the European Medicines Agency as a treatment of relapsing-remitting multiple sclerosis (RRMS). However, with regards to its safety profile, French regulators have limited its use to radiologically and clinically active and severe cases only.

**Objectives:** To describe the efficacy and safety profile of alemtuzumab in a monocentric cohort of patients.

**Methods:** We prospectively collected clinical and radiological data of RRMS patients treated with alemtuzumab since January 2015.

**Results:** 19 RRMS patients (16 women/3 men) received alemtuzumab (mean age at treatment: 34.5 years). Mean disease duration was 11.5 years (range: 2.5-26) and mean EDSS was 4.8 (range 0-8) at treatment onset. In the year before, mean number of relapses was 1.6 (range 1-5). Pre-treatment MRI showed new T2 lesions in 91% and Gadolinium-enhancing lesions in 82% of patients. Mean number of previous disease modifying

treatments (DMT) before alemtuzumab was 4 (2-7). Among 18 patients followed for at least one year, 15 did not relapse and mean EDSS decreased by 0.5. New T2 lesions and new Gadolinium-enhancing lesions were found in 40 % (from 1 to 30 G + lesions / patient). At two years, 9/11 patients had no relapse and mean EDSS decreased by 0.7. New T2 lesions and new Gadolinium-enhancing lesions were found in respectively 36 % and 18 % of the patients (from 8 to 14 G + lesions/patient). Infusion-related reactions were found in 85% of the patients (mainly rash and headache/pyrexia). Noteworthy, 8 patients presented short-term moderate to severe adverse events: 4 episodes of bradycardia (25-45 pulses/mn), 1 pleural and pericardial effusion associated to hepatic cytolysis, 1 pericarditis, 1 spontaneous multiple cervical artery dissection complicated by ischemic stroke and 1 intra alveolar haemorrhage. After 2 years, 1 patient had severe immune thrombocytopenia and neutropenia and 2 patients developed thyroid disorders.

**Conclusion:** Our experience emphasizes the possible modified efficacy and safety profile of alemtuzumab when used as a rescue therapy, rather than in its original early indication, in patients previously exposed to many other DMTs. Further evaluations are warranted to support this assumption.

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### EP1619

#### Impact of dimethyl fumarate (DMF) treatment on immune tolerance during multiple sclerosis

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**Background:** Dimethyl fumarate (DMF) is a first line oral treatment of relapsing-remitting multiple sclerosis (RR-MS) patients. Recent data have shown that DMF inhibits immune cells and inflammation, and may have antioxidant properties protective against damage to the brain and spinal cord during MS. However, the precise molecular mechanism of action of DMF, particularly in the context of its impact on cells involved in immune tolerance such as FoxP3<sup>+</sup> regulatory T cells (Treg cells), remains speculative.

**Objectives:** The aim of this study is to evaluate the capacity of DMF to modulate the peripheral blood immune phenotype and the proliferation and suppressive function of conventional T (Tconv) and Treg cells in RRMS patients.

**Methods:** We obtained blood samples from 22 naïve-to-treatment and 72 previously treated with IFN-beta-1a RRMS

patients and performed an ex vivo immune-phenotyping before and after treatment with DMF. In addition, we analyzed isolated Tconv and Treg cells from RR-MS subjects before and after DMF treatment.

**Results:** We observed that DMF treatment was able to reduce the number of total lymphocytes and of CD3<sup>+</sup>, CD4<sup>+</sup> and CD8<sup>+</sup> T cells. The analysis also revealed that DMF treatment resulted in a specific decrease of cells of the memory compartment (CD3<sup>+</sup>CD45RO<sup>+</sup> and CD4<sup>+</sup>CD45RO<sup>+</sup>). The analysis of proliferation and suppressive function of Treg cells showed that DMF is able to increase the suppressive function of Treg cells with little impact on their proliferative capacity.

**Conclusions:** Our data suggest that DMF could be involved in the control of immune tolerance during MS by reducing the compartment of memory T cells that likely contain the self-reactive fraction of cells, and by increasing the suppressive capacity of Treg cells.

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### EP1620

#### Inhibition of mitochondrial respiration with teriflunomide modulates antigen-specific immune responses in an affinity-dependent fashion

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Teriflunomide (TF) is an immunomodulatory drug used for treatment of T cell mediated autoimmune diseases e.g. rheumatoid

arthritis and multiple sclerosis. Its capacity to inhibit the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH) of the *de novo* pyrimidine synthesis pathway results in a reduced proliferation of activated immune cells. Pharmacological DHODH inhibition via TF interferes with mitochondrial respiration and glycolysis in T cells. Here, we provide first evidence that TF suppresses

T cell proliferation and metabolism in an affinity dependent manner as high affinity T cells were more susceptible towards DHODH inhibition than low affinity T cells. Kinetics of high affinity T cell activation revealed that they increase mitochondrial respiration more rapidly than low affinity T cells in the early phase of activation which explains their enlarged susceptibility towards DHODH inhibition. In an antigen-driven mouse model for central nervous system (CNS) autoimmunity we could illustrate that leflunomide (precursor of TF) treatment results in a preferential reduction of high-affinity T cells and hence in a reduction in mean T cell receptor (TCR) affinities. We therefore hypothesize that DHODH inhibition *in vivo* results in an altered T cell clonal repertoire, a concept which is further supported by recent data from a clinical trial employing the DHODH inhibitor teriflunomide in relapsing-remitting multiple sclerosis (RRMS) patients (TERIDYNAMIC trial). Taken together, our data suggest that the affinity of the peptide-TCR-interaction directs the mode of energy production in T cells and can hence be specifically targeted via DHODH inhibition.

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TT: Employee of Sanofi Genzyme.

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## EP1621

**Should lesions enhanced by gadolinium injection predict efficiency of first line therapies?**

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**Background:** Immunomodulatory treatments are indicated as first line therapy in MS patients after the first demyelinating event. Correlation of MR activity in such patients especially enhanced lesions and response to 1<sup>st</sup> line therapies is not known.

**Objectives:** To evaluate correlation of MR activity and response to first line therapies in MS patients.

**Material and methods:** Based on EDMUS data bank, we retrospectively included MS patients treated by a first line treatment followed during 2 years. Criteria analysis were annual rate of relapses (ARR) and EDSS score at year 1 and 2, compared between patients without (Gd-) and with (Gd+) activity at the baseline MR examination. Extensive follow at 5 years was available in a part of the patients.

**Results:** From 2180 MS patients included in our MS base (EDMUS), 149 MS had inclusion criteria: 91 Gd- and 58 Gd+. Group Gd- characteristics were: sex ratio (M 19 / F 72), mean age of onset: 32.3, mean follow-up: 72 months. Mean EDSS score at the beginning of therapy was 0.7. Most of them (94 %) had an EDSS score below 2. Mean duration of first line therapy was 39.6 months. Gd+ group consisted of 58 patients (M12 / F 46), mean age of onset 31.3 yo, mean follow-up: 60 months, mean EDSS score at the prescription: 0.9 (91 % < 2), duration of treatment: 32.1 months.

At year 1, ARR was 0.35 in Gd- and 0.49 in Gd+ group, mean EDSS score 0.7 and 0.87 (not statistically significant). At year 2, ARR was 0.25 in Gd- and 0.35 in Gd+ patients, mean EDSS score 0.7 and 1.06 (NS). At year 5, EDSS score was available for 54 patients of Gd- group and 29 from Gd+. It was respectively 0.6 and 1.6 (p < 0.05).

**Conclusions:** Occurrence of enhanced lesions on MR at the onset of the first line therapy, suggests a more severe evolution. ARR and mean EDSS score is slightly more important at year 1 and 2 in Gd+ patients. Long term EDSS score is worst in Gd+ patients treated by first line therapy. These results could suggest to treat some MS patients with Gd+ lesions directly by a 2<sup>nd</sup> line therapy.

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## EP1622

**Comparative efficacy of teriflunomide versus dimethyl-fumarate: a French multicenter observational study from the french national OFSEP cohort**

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**Background:** Both Teriflunomide (TRF) and Dimethyl-Fumarate (DMF) have been approved as first line treatments for patients with relapsing-remitting multiple sclerosis (RRMS). However, to date, neither randomized controlled nor observational studies have compared their relative efficacy.

**Objective:** To compare TRF and DMF efficacy on both clinical and MRI outcomes in RRMS patients from the national french OFSEP cohort.

**Methods:** RRMS Patients were included if aged 18 to 65 with an EDSS score of 0 to 5.5 at baseline and an available brain MRI performed within the year before treatment initiation. Data were collected prospectively for 585 patients treated with TRF and 890 with DMF. The main outcome was the proportion of patients with at least one relapse in the year following TRF or DMF initiation. Three secondary endpoints were studied: the proportion of patients with at least a new T2 lesion, the proportion of patients with at least one gadolinium positive (gado+) lesion and the proportion of patients with an increased EDSS score after one year of treatment. Outcomes were modeled using propensity scores (Inverse Probability Weighting) and logistic regressions by using weighted likelihood maximization and robust variance estimator.

**Results:** Baseline comparison revealed that patients treated with DMF were significantly younger with shorter disease duration, increased percentage of patients with at least one relapse in the year and the two years preceding treatment initiation and increased

percentage of patients with at least one gado+ lesion on baseline MRI scans. However, the confounder-adjusted proportion of patients with at least one relapse within the first year of treatment was similar in TRF-treated patients compared to DMF group (20.1% versus 20.4%). On the same way, analyses of the MRI and EDSS secondary endpoints revealed similar efficacy of the treatments at one year after initiation.

**Interpretation:** In France neurologists preferentially choose DMF as a first-line treatment for patients with objective clinical and radiological signs of activity. However, after one year of treatment and after correction for confounders, the efficacy of DMF and TRF was similar in terms of prevention of relapse and occurrence of new T2 or gadolinium-positive lesions.

### Disclosure

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**B Brochet:** consultancy fees, speaker fees, research grants (non-personal), or honoraria from Novartis, Biogen-Idec, Merck, Bayer Schering, Roche, Medday, Bayer, Actelion, Teva and Genzyme Sanofi.

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**C. Pottier:** Research supports from Novartis

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**Y Foucher:** nothing to disclose

**E Leray:** nothing to disclose

### EP1623

#### Real clinical experience in multiple sclerosis patients treated with alemtuzumab in the Northwest of Spain

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Universitario de Ferrol, Ferrol, <sup>10</sup>Complejo Hospitalario

Universitario de Ourense, Ourense, <sup>11</sup>Hospital Universitario

Lucus Augusti, Lugo, Spain

**Background:** In pivotal studies alemtuzumab have demonstrated a marked reduction of relapse rates and improved on MRI outcomes. Different results were obtained about disability.

**Objectives:** To describe “real-world” experience of the use of alemtuzumab in a multicentre cohort of patients.

**Methods:** Patients from 11 centres from the Northwest of Spain who received first dose Alemtuzumab were included. Baseline and prospective data were obtained. Previous disease-modifying

treatment (DMT) use and reason for changing to Alemtuzumab, relapse rate, EDSS change and magnetic resonance imaging (MRI) are described. EDSS were performed at baseline and every 6 months. The reported cranial MRI scans were performed at baseline and annually.

**Results:** Eighty three patients: 55 (66%) females and 28 (34%) males, were included. Mean of age was  $39.4 \pm 8.27$  years. Mean duration of follow up was  $11.0 \pm 5.88$  months; 30 patients received the second course. Mean MS duration was of  $10.8 \pm 6.86$  years. Annualized relapse rate (ARR) in the previous year was  $1.3 \pm 1.13$  and mean baseline EDSS was  $3.5 \pm 1.66$  (median 3.5). The mean number of previous DMT was  $2.5 \pm 1.51$ . The main reason for switching to alemtuzumab was lack of efficacy (80%). The 28 patients who was followed for 12 months, showed an important reduction of ARR, from  $1.82 \pm 1.36$  to  $0.07 \pm 0.26$  ( $U=319.5$ ;  $p < 0.001$ ); and mean EDSS did not change. From baseline to 12 months, there was a reduction from 58% to 15% ( $n=26$ ) in the number of patients with gadolinium-enhancing lesions on T1-weighted MRI and there were 23% of patients with new T2-hyperintense lesions ( $n=26$ ). Infusion-related reactions were registered in 67 (81%) patients (all were mild-moderate). Infections were detected in 33% of patients; the most common were urinary tract infections. Thyroid disease was the only observed secondary autoimmune disorder (6% of patients). No serious adverse events (AE) occurred.

**Conclusions:** This study confirms a positive effect on clinic (relapses, EDSS) and radiological measures. AE are predictable and treatable. Thyroid disease was the only autoimmune disorder observed.

## Disclosure

López Real A.M. has served as speaker for Biogen Idec, Merck Serono, Genzyme, Novartis and TEVA;

Peña Martínez J. has served as speaker for Sanofi Genzyme, Merck, Bayer, Teva, Biogen Idec, Novartis, Almirall, Krka and Qualigen;

Rodríguez Regal A has served as speaker for Genzyme, Biogen and TEVA.

Oterino Duran A., has served as speaker for Biogen, Almirall, Merck, Teva, Sanofi-Genzyme, Allergan, MSD and Novartis.

Solar Sanchez D.M. has served as consultant for Almirall, Biogen, Bayer, Merck, Novartis, Sanofi-Genzyme, TEVA;

Pato Pato A. has received grants for clinical research from Biogen, Novartis, Genzyme, Almirall, Bayern;

Gonzalez Suarez I. has received grants from Biogen, Novartis, Genzyme;

Garcia-Pelayo Rodriguez A.M. has served as speaker for Merck Serono and Genzyme.

Costa Arpín E.: has served as speaker or consultant for Biogen Idec, Merck Serono, Bayer Health Care, Genzyme, TEVA and UCB Pharma;

Llaneza Gonzalez M. has served as speaker for Sanofi-Genzyme, Biogen, Novartis, Teva, Merck, Almirall;

García Bargo M.D. has served as speaker for Sanofi Genzyme;

Rodríguez Rodríguez M has served as speaker for Sanofi, Biogen, Merck, Novartis and TEVA;

Prieto González J.M. has served as advisor, consultant and speaker for Bayer HealthCare Pharmaceuticals, Biogen Idec Inc, Genzyme Corporation, Novartis, Sanofi and Teva. He also has received

grants for clinical research from Biogen Idec Inc and Novartis Pharmaceuticals Corporation.

## EP1624

### Comparison of the B-cell recovery time following discontinuation of anti-CD20 therapies

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<sup>1</sup>Novartis Pharma AG, Basel, Switzerland, <sup>2</sup>Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

**Background:** The success of anti-CD20 monoclonal antibodies (mAbs) in clinical trials highlights a key role for B-cells in driving multiple sclerosis (MS) pathology and disease activity. Anti-CD20 mAbs differ in terms of epitope binding, potency and dosing regimen. Due to its unique biological properties, the fully human mAb ofatumumab (OFA) is given as subcutaneous (s.c.), low dose, monthly injections as maintenance therapy in ongoing Phase 3 studies.

**Objective:** To evaluate the B-cell recovery time after discontinuation of OFA compared with other anti-CD20 therapies.

**Methods:** We used the MIRROR Phase 2 dose-ranging study of s.c. OFA in relapsing-remitting MS (RRMS), which included a 24-week treatment phase and a 24-week follow-up, to describe B-cell repletion for OFA at different doses and administration frequencies in comparison with previously published results for intravenous (i.v.) ocrelizumab (OCR) and i.v. rituximab (RTX). In addition, we used a population kinetics-pharmacodynamic model developed using MIRROR data to predict time to B-cell repletion after OFA treatment stop. These predictions were done under conditions of the current OFA Phase 3 trials and compared with the published OCR data.

**Results:** The successful depletion of peripheral CD19<sup>+</sup> B-cell counts by OFA, OCR and RTX has been reported previously. For OFA, median time to repletion (CD19<sup>+</sup> B-cell count above the lower limit of normal or  $\geq$ baseline value) in weeks from last active dose was 36.7 (7.6, 97.1) for 30 mg every 12 weeks (Q12W), 36.1 (12.1, 111.0) for 60 mg Q12W, and 49.0 (14.4, 101.9) for 60 mg Q4W. For the humanised mAb OCR, median time to B-cell repletion was 71.0 weeks (95% CI: 59-76 weeks). Repletion of immature B-cells (CD19<sup>+</sup>CD27-IgD<sup>+</sup>CD38<sup>+</sup>bCD10<sup>+</sup>) to baseline occurred within 4 weeks with OFA. For RTX, a chimeric mAb, the naïve B-cell population (CD27-IgD<sup>+</sup>) slowly increased, reaching baseline only after 12-16 months. Our model-based predictions showed that by week 38 since last dose of OFA (loading of 20 mg three times weekly followed by 20 mg Q4W), 50% of patients repleted to either  $\geq 110$  B-cells/ $\mu$ l or baseline compared with 11% for OCR 600 mg.

**Conclusions:** OFA differs from other anti-CD20 therapies as it achieves faster post-treatment B-cell repletion. Faster repletion may be beneficial in the management of adverse events or in treatment sequencing. As the present analysis is based on a 24-week OFA treatment duration, B-cell recovery times may need to be confirmed after longer-term dosing.

## Disclosure

Marina Savelieva, Joseph Kahn, Morten Bagger, Daniela Piani Meier, Davorka Tomic, David Leppert, and Erik Wallström are



currently employees of Novartis. As of 1<sup>st</sup> July 2017, Erik Wallström will be employed by Sanofi.

#### EP1625

##### **Lymphocyte recovery in real life clinical practice after discontinuation of fingolimod in patients with multiple sclerosis**

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*University Hospital Basel, Basel, Switzerland*

**Background and aims:** Fingolimod induces a fast reduction of lymphocyte counts in the blood, however, less is known about the recovery of immune cells after treatment discontinuation in real life clinical practice, especially in patients who begin with a new immunomodulatory treatment shortly after cessation of fingolimod. Therefore, we aimed to analyze the course of lymphocyte recovery and its potential influencing factors in the first year after fingolimod discontinuation in patients with multiple sclerosis.

**Methods:** We examined leukocyte, lymphocyte and neutrophil counts of 58 patients with multiple sclerosis, 3 (mean  $79.1 \pm 31.6$  days), 6 (mean  $193.3 \pm 35.7$  days) and 12 (mean  $368.6 \pm 48$  days) months after cessation of fingolimod. Blood tests were available in 55 patients for the baseline (prior fingolimod), in 47 patients for the 3 months, in 46 for the 6 months and in 48 for the 12 months time-point. Leukopenia was defined as  $\leq 3500$ , lymphopenia as  $\leq 900$ , neutropenia as  $\leq 1300$  cells per microliter. We included age, sex, EDSS and disease duration at fingolimod start, fingolimod treatment duration, transition time before therapy switch, lymphocyte baseline prior fingolimod and at start with a following medication, and previous immunomodulatory regimens into our analysis.

**Results:** All patients showed a drop of lymphocyte count under fingolimod with no relevant leukopenia or neutropenia. Three months after fingolimod discontinuation 11 patients showed decreased lymphocyte levels (23.4%), while six and twelve months later still 10 patients were lymphopenic (21.7%). 8 out of these 10 patients received rituximab as a follow-up treatment. 47% (8 out of 17) patients that switched to rituximab and 3 out of 4 patients pretreated with mitoxantrone showed delayed lymphocyte recovery. Patients with prolonged lymphopenia had a longer treatment duration of fingolimod and tended to have lower lymphocyte counts at baseline and at therapy switch.

**Conclusion:** Only 42% of patients reached their baseline lymphocyte levels, while 21.7% stayed lymphopenic after one year of cessation of fingolimod. Longer treatment duration of fingolimod, low lymphocyte counts at baseline and at therapy switch, successive treatment with rituximab, and pretreatment with mitoxantrone might contribute to a prolonged immune cell recovery and should be considered when changing treatment regimens.

#### **Disclosure**

The institution (University Hospital Basel) received in the last 3 years and used exclusively for research support: steering committee, consulting and speaker fees from Actelion, Addex, Bayer HealthCare, Biogen, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono, Pfizer, Receptos, Sanofi-Aventis, Santhera, Siemens, Teva, UCB and Xenoport; support of educational activities from Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi-Aventis and Teva; royalties from

Neurostatus Systems GmbH; grants from Bayer HealthCare, Biogen, the European Union, Merck, Novartis, Roche, the Swiss Multiple Sclerosis Society and the Swiss National Research Foundation.

#### EP1626

##### **Real world effectiveness and safety of alemtuzumab in MS patients**

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<sup>1</sup>Hospital Universitario Virgen Macarena, <sup>2</sup>Hospital Universitario Germans Trias i Pujol, Sevilla, Spain

**Background:** Alemtuzumab has shown high efficacy in decreasing relapse rates in patients with active relapsing MS in clinical trials, but data from real world clinical practice is needed to confirm these findings.

**Goal:** To study efficacy and safety outcomes in real world patients treated with alemtuzumab.

**Methods:** Patients with highly active RRMS treated with alemtuzumab since March 2015 at Virgen Macarena Hospital, Sevilla, Spain. Baseline, MS characteristics, relapses, change in disability, and adverse event data in alemtuzumab-treated patients were collected.

**Results:** 65 patients (43 females, 66%) were identified with a mean follow-up of 13.3 months (28-3). 31 (48%) have received their second course of treatment.

Average age was 39.4 years (range 20-60) and the mean years since MS diagnosis was 15.2 (range 3-30). Patients had been treated with a mean of 2.3 disease modifying therapies prior to alemtuzumab treatment. Following alemtuzumab treatment, the annualized relapse rate (ARR) decreased from 1.6 to 0.09, and EDSS decreased from a mean of 4.6 to 4.0. 34 (59.6%) patients showed lower EDSS values, 22 (38.6%) patients showed stable EDSS, and 1 (1.7%) showed an increase in EDSS. 3 patients (4.6%) had relapses after receiving the first course of alemtuzumab (with active MRI), and one of them was treated with the second course 10 months after the first. This patient is currently the only candidate for re-treatment.

All patients were treated with the second course of alemtuzumab when their lymphocyte counts were normal, with a mean of 12.7 months post first course (10-16). 89% had mild to moderate infusion reactions during the first course, with 77% experiencing mild infections within the first year on treatment. One patient suffered a severe cytomegalovirus and pneumocystis jirovecii pneumonia infection, but recovered following antibiotic treatment. 13% of patients developed thyroid disorders between the two courses; 3 cases of hypothyroidism and 5 cases of hyperthyroidism, 2 of which required a thyroidectomy.

**Conclusions:** Our data shows that MS patients treated with alemtuzumab in a real world clinical setting show significant decreases in ARR and the majority maintain or improve their disability. Mild to moderate infusion reactions and manageable adverse events were observed.

#### **Disclosure**

Sara Eichau received speaker honoraria and consulting fees from Genzyme, Biogen, Merck Serono, Teva and Novartis

**EP1627****Baseline characteristics and safety profile of patients in the first interim analysis of the peginterferon beta-1a Phase IV POP study**

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**Background:** Subcutaneous peginterferon beta-1a 125 mcg every 2 weeks is approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). The 5-year observational Phase IV Plegridy Observational Study (POP) provides an opportunity to explore the long-term safety and effectiveness of peginterferon beta-1a in a real-world setting.

**Objectives:** Report interim data on baseline, adverse events (AEs), and clinical effectiveness from the POP study.

**Methods:** The POP study is ongoing in over 150 sites in 14 countries. Patients who initiated peginterferon beta-1a treatment either after or within 31 days prior to date of consent (Naïve subgroup) and patients treated with peginterferon beta-1a more than 31 days prior to date of consent (Experienced subgroup) will be followed for up to 5 years.

**Results:** Data from 467 patients treated with peginterferon beta-1a were analysed. At the time of this first interim analysis, 409 patients (88%) had been followed for 12-24 months. A total of 153 patients (31%) discontinued treatment, primarily due to AEs (55%) and lack of efficacy (13%). At on-study baseline, mean age was 44.9 years, 76% were female, and the mean Expanded Disability Status Scale (EDSS) score was 1.9. Of the 370 patients (79%) previously treated with a disease-modifying therapy, 217 (46%) had been treated with intramuscular interferon beta-1a. There were more patients in the Naïve subgroup than in the Experienced subgroup (60% vs 40%, respectively). Overall, AEs were more common in the Naïve subgroup compared with the Experienced subgroup (35% vs 20%). Serious AEs were reported in 5% and 9% of the Naïve and Experienced subgroups, respectively. AEs leading to treatment discontinuation were also more common in the Naïve subgroup (29% vs 15%). The most commonly reported AEs leading to treatment discontinuation in both groups were injection-site erythema and influenza-like illness. A high proportion of patients in both groups were reported to be relapse-free (84.4% and 81.5%; Naïve and Experienced, respectively).

**Conclusions:** The safety profile reported in this first interim analysis of the POP study was consistent with that observed in the pivotal Phase 3 trial of peginterferon beta-1a. No new safety signals were observed. Patients who had been naïve to peginterferon beta-1a were more likely to experience AEs and discontinue treatment due to injection site reactions and flu-like symptoms, highlighting a need for prophylactic mitigation strategies.

**Disclosure**

Marco Salvetti has received grant support and speaker honoraria from Biogen.

Andrew Pachner has been a PI on clinical trials funded by: Biogen, EMD Serono, Genzyme, Novartis, Genentech, and

Roche; as well as a PI on basic research studies funded by: Acorda, Biogen, EMD Serono and Genzyme. He has received consulting fees for participation in advisory boards from Biogen, Genzyme, and Novartis.

Jang Yun, David Appiah-Badu, Guido Sabatella, and Maria L. Naylor are employees and stockholders of Biogen.

**EP1628****Halting disability progression in multiple sclerosis with immunomodulatory injectable treatments: Is it achievable?**

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**Introduction:** The introduction of newer therapies for the treatment of multiple sclerosis (MS) is based upon the need to control neurological disability. Halting disability progression is a challenge for therapy since permanent neurological impairment is the most worrisome aspect of MS for patients and their doctors. The objective of this study was to identify whether "older" injectable treatments can lead to MS-related disability control over at least seven years.

**Materials and methods:** Data were sourced from the MSBase Registry Patients with at least seven years of continuous treatment with any formulation of interferon beta or glatiramer acetate were analyzed. Disability control was defined as no increase in the expanded disability scale score (EDSS) >1-point from baseline. Time to event by index DMT product was analysed via Cox proportional hazards regression.

**Results:** Of the 546 eligible patients, 379 (69.4%) were female with a mean (SD) age and disease duration at index DMT start of 38.2 years (10.3) and 7.3 years (7.2) respectively. Median (IQR) EDSS at baseline was 2. A total of 225 patients (41.2%) recorded a minimum greater than 1-point increase from their baseline EDSS, sometime during their on-index treatment follow-up. The remaining 321 patients (58.8%) maintained the "disability control" state during follow-up. Median time to event (>1-point increase from baseline) was 12.3 years. There were no significant differences in time to EDSS increase among the different formulations of interferon beta and/or glatiramer acetate.

**Conclusion:** Patients with MS who respond well to immunomodulatory injectable treatments may exhibit satisfactory control of neurological disability over long-term follow-up.

### Disclosure

Yara Dadalti Fragoso, Tim Spelman, Pierre Duquette, Marc Girard, Maria Trojano, Guillermo Izquierdo, Pierre Grammond, Alessandra Lugaresi, Vincent Van Pesch, Francois Grand'Maison, Celia Oreja-Guevara, Gerardo Iuliano, Roberto Bergamaschi, Maria Edite Rio, Ricardo Fernández Bolaños, Murat Terzi, and Helmut Butzkueven, have no particular conflicts of interest to declare for this abstract. The work was carried out on behalf of MSBase study group, which receives unconditional grants from pharmaceutical industries (Biogen Idec, Novartis, MerckSerono, Genzyme) to support the existence of the database.

### EP1629

#### Effectiveness of fingolimod in Spanish patients with relapsing-remitting multiple sclerosis in the clinical practice

V. Meca-Lallana<sup>1</sup>, S. Martínez Yélamos<sup>2</sup>, J. Mallada<sup>3</sup>, J. Meca-Lallana<sup>4</sup>, M. Martínez<sup>5</sup>, E. Marzo<sup>6</sup>, C. Durán<sup>7</sup>, T. Ayuso<sup>8</sup>, F. Barrero<sup>9</sup>, R. Romero<sup>10</sup>, R. Guillen<sup>10</sup>, J. Ricart<sup>10</sup>, E. García<sup>10</sup>, MS NEXT and MS SECOND LINE GATE studies

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**Background:** Fingolimod is a sphingosine 1-phosphate receptor modulator for relapsing-remitting multiple sclerosis RRMS treatment. Continuous collection and analysis of real world effectiveness and safety data is key to making accurate treatment decisions.

**Objective:** To describe baseline characteristics at fingolimod treatment initiation and effectiveness of fingolimod in RRMS patients in clinical practice.

**Methods:** Pooled analysis of 2 observational, retrospective, multicentre studies conducted in Spain: MS SECOND LINE GATE and MS NEXT. Both studies were carried out in RRMS patients, ≥18 years, treated with 0.5mg/day of fingolimod and followed for ≥1 year after treatment initiation.

**Results:** 988 patients were included (post first-line injectable disease-modifying treatment [iDMT]: 666 patients, post-natalizumab [NTZ]: 252, treatment-naïve: 70; 69% female, mean [SD] age: 40 [9] years). At year 1, 2 and 3 after treatment initiation, mean annual relapse rate (ARR) decreased by 77%, 82% and 86% compared to the year prior to treatment initiation ( $p < 0.0001$  all). At year 3, mean ARR significantly decreased in iDMT and treatment-naïve subgroups by 91% and 96%, respectively, and remained stable in NTZ patients. At year 1, 90% of patients had stable or improved EDSS that was maintained in 84% of patients at year 2. Mean number of T1 Gd+ lesions decreased significantly in the overall population: 69% (year 1) and 80% (year 2) ( $p < 0.0001$ ). At year 1 and year 2, 72% and 58% of patients did not show new/increased T2 lesions respectively, and 78% and 69% were relapse-free.

**Conclusions:** Fingolimod is an effective treatment for RRMS in the clinical practice. At year 3, there was a decrease in the

mean ARR of treatment-naïve and iDMT patients, and stabilization in NTZ patients. After fingolimod treatment initiation, RRMS patients significantly improved clinical disease activity and most of the patients had a stable EDSS after one year of treatment.

### Disclosure

V. Meca-Lallana: has received honoraria and travel expenses for scientific meetings and has participated in advisory boards in the past years with: Almirall, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, TEVA and Terumo

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F. Barrero: has received consulting/speaker fees from and advisory board for Bayer HealthCare, Biogen, Genzyme, Merck Serono, Novartis, Roche, Sanofi-Aventis, and Teva, and been involved with clinical trials for Novartis.

R. Romero: Novartis employee

R. Guillen: Novartis employee

J. Ricart: Novartis employee

E. García: Novartis employee

### EP1630

#### Delayed-release dimethyl fumarate demonstrated no difference in clinical outcomes versus fingolimod in patients with relapsing-remitting multiple sclerosis: results from the real-world EFFECT study

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**Background:** In real-world comparative effectiveness studies of relapsing-remitting multiple sclerosis (RRMS) patients, including claims data and registries, treatment with delayed-release dimethyl fumarate (DMF) compared with fingolimod (FTY) for up to 2 years was associated with no statistically significant differences in relapse outcomes.

**Objectives:** To report the real-world effectiveness of DMF compared with FTY in RRMS patients (pts) at 12 months.



**Methods:** EFFECT (NCT02776072) was an observational, multi-centre, international, retrospective, single time point, medical record review study undertaken to evaluate the effectiveness of DMF and other disease-modifying therapies (DMTs). Pt eligibility criteria included: age  $\geq 18$  years, diagnosis of RRMS, treatment naïve or 1 prior DMT (interferon or glatiramer acetate [GA]), initiation of DMT treatment after December 2010, and  $\geq 12$  months of medical record data following DMT initiation. Endpoints included Kaplan-Meier estimated proportion of pts relapsed at 12 months and annualized relapse rate (ARR). Substantive baseline covariates were used in estimating propensity score. The data were divided into

4 strata using quartiles of propensity score. After assessing for balance in baseline covariates between treatment groups, Kaplan-Meier estimates and estimate of treatment effects were pooled across strata of propensity score.

**Results:** Of the 826 DMF and 785 FTY pts enrolled at sites in 17 countries, 816 and 781 pts, respectively, were included in the full analysis set. Treatment groups were balanced after propensity score stratification. At 12 months, 86% of DMF-treated patients and 94% of FTY-treated patients remained on therapy. In the trimmed full analysis set, the estimated proportion of DMF pts that relapsed at 12 months was 12% compared with 13% for FTY pts; hazard ratio (95% CI) 1.07 (0.78, 1.46;  $p=0.6926$ ). At 12 months after treatment initiation, the adjusted ARR ratio (95% CI) was 1.09 (0.80, 1.49;  $p=0.5754$ ) for pts treated with DMF compared to FTY.

**Conclusions:** Over 12 months, treatment with DMF versus FTY was associated with no statistically significant difference on relapse outcomes.

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**Okwukenye M:** Employee of and holds stock/stock options in Biogen

**Taylor C:** Employee of and holds stock/stock options in Biogen

## EP1631

**Delayed-release dimethyl fumarate significantly reduced relapse based outcomes vs. interferon, glatiramer acetate, or teriflunomide: pairwise propensity-matched comparative effectiveness analyses of the German NeuroTransData registry**

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**Background:** There are currently no head-to-head, randomized controlled trials comparing efficacy outcomes between delayed-release dimethyl fumarate (DMF) vs interferon (IFN), or teriflunomide (TERI) in patients with relapsing-remitting multiple sclerosis (RRMS) whilst evidence for comparison vs GA is limited to the CONFIRM study (Fox et al. N Engl J Med. 2012).

**Objective:** To assess the comparative effectiveness of delayed-DMF vs IFN, GA, or TERI in a pair-wise propensity-score-matched (PSM) cohort of patients with RRMS as measured by the primary outcome of time to first relapse (TTFR) and the secondary outcomes of annualized relapse rate (ARR), time to treatment discontinuation (TTD), and time to 3- and 6-months expanded disability status score (EDSS) confirmed disability progression (TTCDP3, TTCDP6).

**Methods:** Data were sourced from the NeuroTransData (NTD) MS registry, a German network of >130 practice-based neurologists and including ~25,000 MS out-patients. As of 01 October 2016, patients with RRMS aged  $\geq 18$  years at therapy initiation with  $\geq 1$  relapse or EDSS assessment on-therapy were included; 1:1 PSM was used to match DMF to comparator cohorts. TTFR, TTD and TTCDP3/6 were analyzed using a Kaplan-Meier approach and Cox-marginal-regression-model. ARR was analyzed using a GEE Poisson-regression-model. The clustered nature of the matched design was taken into account. Non-pairwise censoring was applied with a pre-defined sensitivity analysis using pairwise censoring.

**Results:** DMF patients were matched 1:1 to IFN ( $n=439$ ), GA ( $n=535$ ), and TERI ( $n=388$ ) patients; more than 75%, 61%, and 36% were treatment-naïve, respectively. Time-to-first relapse was significantly reduced for DMF vs IFN (hazard ratio [HR] 0.59; 95% confidence interval [CI] 0.44, 0.79;  $p=0.0004$ ), GA (HR 0.65; 95% CI 0.50, 0.84;  $p=0.0011$ ) and TERI (HR 0.53; 95% CI 0.38, 0.75;  $p=0.0003$ ). ARR was significantly reduced for DMF vs IFN (Rate ratio (RR) 0.71; 95% CI 0.53, 0.94;  $p=0.017$ ), GA (RR 0.76; 95% CI 0.59, 0.98;  $p=0.035$ ) and TERI (RR 0.55; 95% CI 0.39, 0.77;  $p=0.001$ ). A sensitivity analysis using pairwise censoring was conducted demonstrating consistent results with the primary analyses. No differences in time to TTCDP3/6 and TTD were evident for any comparison.

**Conclusions:** Time-to-first relapse and ARR were significantly reduced in patients treated with DMF vs IFN, GA, and TERI in pairwise propensity-score matched populations from the NTD network.

## Disclosure

Braune S, Bergmann A and most of the members of NTD study group receive royalties from many pharmaceutical companies for participation in clinical trials, lecturing, consultancy. For this NeuroTransData own project there is no conflict of interest. van Hövell P, Grimm S are fulltime employees of PwC and have no conflict of interest.

Hyde R and Freudensprung U are fulltime employees and stockholders in Biogen.

## EP1632

**Comparison of natalizumab vs fingolimod and dimethyl fumarate in the treatment of multiple sclerosis: two year experience**

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**Objective:** Compare two year discontinuation rates and efficacy of fingolimod (FTY) and dimethyl fumarate (DMF) to natalizumab (NTZ).

**Background:** FTY and DMF are the most common MS oral therapies becoming available in 2010 and 2013, respectively. Limited comparative effectiveness data exists.

**Methods:** Patients prescribed FTY, DMF or NTZ at the Rocky Mountain MS Center at University of Colorado between January, 2010 and October, 2013 were identified. Clinician-reported data including demographics, disease history, relapses, MRI outcomes, and adverse events (AEs), were retrospectively collected. Primary outcome was the probability of discontinuing drug within two years, which is presented here. Data was analyzed with logistic regression controlling for age, disease duration, type of MS, gender, and presence of enhancing lesions on baseline MRI to estimate differences in the primary outcome.

**Results:** 271, 342 and 451 patients were evaluated on FTY, DMF and NTZ over two years. Patients had a mean age of 42.5 (FTY), 45.8 (DMF) and 39.8 (NTZ) years; were predominantly female (72.0% FTY; 69.6% DMF; 76.7% NTZ); and had a mean MS disease duration of 11-12 years for all groups. At  $\leq 24$  months, 93 (34.3%), 161 (47.1%) and 147 (32.6%) discontinued FTY, DMF and NTZ, respectively. FTY versus NTZ had an adjusted OR of 1.18 (95%CI: 0.85 - 1.65,  $p = 0.315$ ) for discontinuation at  $\leq 24$  months. DMF versus NTZ had adjusted OR of 2.06 (95%CI: 1.50 - 2.83,  $p < 0.001$ ). Primary reason for discontinuation: NTZ - +JCV antibodies (12.6%), FTY and DMF - adverse events (17.0% and 24.0%). The most common adverse events leading to discontinuation were gastro-intestinal related issues for FTY and DMF, and a rash at time of infusion for NTZ. Respectively for FTY, DMF and NTZ - 24 (8.9%), 44 (12.9%) and 27 (6.0%) had a clinical relapse, 28 (13.1%), 26 (10.0%) and 17 (5.8%) had gadolinium-enhancing lesions and 75 (35.1%), 82 (31.5%) and 74 (25.3%) had new T2 lesions.

**Conclusions:** There were fewer discontinuations with DMF vs. NTZ. Discontinuation rates in the first two years were driven by AEs and being positive for JC virus antibodies. Further analyses will investigate NTZ superiority in efficacy outcomes using propensity matching and ATT doubly robust weighting methods.

## Disclosure

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## EP1633

### Teriflunomide inhibits activation and proliferation of B-cells in patients with relapsing remitting multiple sclerosis (RRMS)

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**Objective:** To investigate the effect of teriflunomide, an approved therapy for RRMS, on the activation and proliferation of B-cells.

**Background:** Teriflunomide is a high affinity inhibitor of dihydroorotate dehydrogenase (DHODH), a key enzyme in pyrimidine synthesis. De-novo pyrimidine synthesis is required by rapidly proliferating cells, such as activated lymphocytes to progress through the cell cycle.

**Methods:** Peripheral blood mononuclear cells (PBMC) were isolated from 20 untreated RRMS patients. Teriflunomide effects on B-cells were studied using *in-vitro* assays. PBMC were stimulated with anti-IgG/IgM and rCD40L in the absence or presence of 100  $\mu$ M teriflunomide and exogenous uridine. Proliferation and surface markers expressions of CD19<sup>+</sup> B-cells were measured using flow cytometry and teriflunomide effect on the signalling pathways in B-cells were analysed using western blotting.

**Results:** In proliferation assay, anti-IgG/IgM and rCD40L treatment for 4 days induced a significant proliferation of CD19<sup>+</sup> B-cells ( $p < 0.001$ , fold change: 1.83), which was inhibited by teriflunomide treatment ( $p < 0.001$ , fold change: 0.87). The addition of exogenous uridine reversed inhibition of CD19<sup>+</sup> B-cell proliferation. Stimulation of CD19<sup>+</sup> B-cells increased the expression of CD25, OX40, CD80, CD5, CD24, and CD20. Teriflunomide treatment down-regulated the expressions of activation markers CD25 ( $p < 0.05$ ) and IgD ( $p < 0.05$ ), B-cell chemokine receptor CCR2 ( $p < 0.01$ ), costimulatory molecule CD80 ( $p < 0.001$ ), and CD5 ( $p < 0.05$ ), which are all reversed in the presence of exogenous uridine. Teriflunomide treatment of activated B-cells inhibited the phosphorylation of p65 ( $p < 0.001$ ), IKK $\alpha$  ( $p < 0.001$ ), pERK 1/2 ( $p < 0.001$ ), pSTAT1 ( $p < 0.001$ ) and pSTAT3 ( $p < 0.001$ ).

**Conclusion:** Teriflunomide inhibits activation and proliferation of B-cells derived from RRMS patients. Inhibition of pSTAT1, pSTAT3, and NF-kappa B signalling, and CD5 and CD80 costimulatory molecule expression may inhibit B-cell cytokine secretion and antigen presenting capacity, while inhibition of CCR2 may decrease B-cell migration to the CNS.

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#### EP1634

##### **Laquinimod protects optic nerve and retina in an experimental autoimmune encephalomyelitis model**

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**Background:** The oral immunomodulatory agent laquinimod is currently evaluated for multiple sclerosis (MS) treatment. The phase III ALLEGRO study demonstrated a reduction of lesion development, brain atrophy, relapse rate and progression of disability with (under?) laquinimod therapy. In addition to anti-inflammatory effects, laquinimod might have neuroprotective properties. However, its impact on the visual system, which is often affected by MS, is unknown.

**Objective:** To investigate a potential protective effect of laquinimod on optic nerve and retina in an experimental autoimmune encephalomyelitis (EAE) model.

**Methods:** We immunized wild-type C57/BL6 mice with MOG<sub>35-55</sub> to induce EAE. Five groups were investigated: an untreated EAE group, three EAE groups receiving laquinimod in doses of 1, 5, or 25 mg/kg daily, starting the day post-immunization, and a healthy control group without EAE. Neurological impairment was evaluated via scoring. 30 days post-immunization, scotopic electroretinograms were carried out and mice were sacrificed for histopathology, immunohistochemistry, and qRT-PCR. In the optic nerve, the extent of cellular infiltration (HE) and demyelination (LFB, MBP) was monitored. Microglia (Iba1) with macrophage function (F4/80) and macroglia (astrocytes, GFAP), including retinal Müller glia (vimentin), were examined in retina and optic nerve. Moreover, we investigated retinal ganglion cells (Brn-3a) and their rates of apoptosis (cleaved caspase-3).

**Results:** Laquinimod significantly reduced clinical EAE symptoms in a dose-dependent manner. In electroretinogram measurements, a protection of neurons in the inner nuclear layer could be noted. Laquinimod decreased signs of cellular infiltration (25 mg:  $p=0.002$ ) and demyelination (25 mg:  $p<0.001$ ) in the optic nerve. Numbers of microglia, also with macrophage function, in optic nerves and retinas, were reduced. Retinal macroglial signal was diminished under treatment, whereas in the optic nerve more GFAP signal was found. Furthermore, laquinimod protected retinal ganglion cells (25 mg:  $p<0.001$ ) and lowered their apoptosis rate (25 mg:  $p<0.029$ ).

**Conclusion:** From our study, we deduce neuroprotective and anti-inflammatory effects of laquinimod on optic nerve and retina in EAE mice. Given the fact that the visual system is frequently affected by MS, the agent might be an interesting subject of further neuro-ophthalmic investigations.

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#### EP1635

##### **Acceptability of first-line disease-modifying drugs in relapsing-remitting multiple sclerosis: a real-life multicenter study**

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Multiple sclerosis (MS) first-line disease-modifying drug (DMD) treatment options now include oral drugs in addition to injectable therapies. Purpose of this multicenter real-life prospective study was to assess the proportion of patients discontinuing a newly initiated first-line treatment, for any reason, during a one-year follow-up period.

Nine MS centres in Emilia-Romagna, Italy, enrolled consecutive MS patients starting any first-line DMD during 2015, and recorded data on treatment discontinuation throughout a one-year period. Five-hundred patients were enrolled in the study (353F, 147M; mean age: 43 years; mean baseline EDSS: 1.8 +/- 1.3), and followed up for at least one year or until the DMD was discontinued (mean: 13 +/- 5 months). An injectable drug (beta-interferon 1a/b, glatiramer acetate) was started in 246 patients (49%) and an oral one (dimethylfumarate, teriflunomide) in 254 (51%); 155 (31%) were treatment-naïve. A total of 113 (23%) patients discontinued the drug, mostly due to adverse events/tolerability issues (54% of cases) or ongoing disease activity (33%). There was no difference in a) the proportion of patients on oral or injectable DMD discontinuing treatment (22% and 24%, respectively), b) the reason for treatment discontinuation, and c) in the time to treatment discontinuation between the two groups. Patients starting oral drugs had



higher basal EDSS values (2.1 versus 1.5,  $p < 0.001$ ), as had treatment-naïve patients (1.9 versus 1.6;  $p = 0.02$ ). Treatment-naïve patients started injectable therapies, as opposed to oral drugs, more frequently (117/155 versus 129/345;  $p < 0.001$ ), and were more likely to discontinue treatment (45/155 versus 68/345,  $p = 0.02$ ).

There was no difference in the acceptability of injectable versus oral first-line DMD in MS patients, as measured by the proportion of patients discontinuing the drug for any reason during the first year of treatment.

## Disclosure

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## EP1636

### Characterizing temporal pattern of alemtuzumab infusion-associated reactions: experience in clinical practice in a multicentre study of the Northwest of Spain

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**Background:** In pivotal studies, Alemtuzumab infusion-associated reactions (IARs) occurred in a majority (>90%) of patients despite using of prophylactic treatment; 3% were serious.

**Objectives:** To describe the most relevant IARs and its temporal pattern in routine clinical practice in 11 centres of the Northwest of Spain.

**Methods:** Eighty three patients: 55 (66%) females and 28 (34%) males, who received first dose Alemtuzumab were included. Mean age was  $39.4 \pm 8.27$  years. The median duration of follow up was  $11.0 \pm 5.88$  months; 30 patients received the second course.

Alemtuzumab infusion was given over approximately 5 hours. Patients received daily previous standardized pre-medication regimen: antihistamines, proton-pump inhibitors, diphenhydramine, acetaminophen and methylprednisolone (MP). 1g MP was administered on infusion day 1-3 of each course and 500 mg on day 4-5. IARs was observed and managed with symptomatic treatments as needed during and post-infusion. All IARs and its severity were collected.

**Results:** IARs occurred in 67 (81%) patients and all were mild to moderate in severity.

The 1<sup>st</sup> infusion day pyrexia and headache were the most frequent IARs. On infusion days 3<sup>rd</sup> to 5<sup>th</sup>, the most prominent IARs were rash and urticaria, being observed until 72 hours after the last infusion day. Similar temporal pattern of IARs was observed in the first and the second courses. IARs were less frequent during course 2 (mean  $2.3 \pm 2.33$  events/patient) than during course 1 (mean  $3.4 \pm 3.45$  events/patient).

**Conclusions:** In our clinical experience, IARs were less frequent than in clinical trials and no serious IARs occurred.

It is interesting to observe that IARs have a characteristic temporal pattern of presentation. Pyrexia and headache were typically observed on the first day. Rash and urticaria were more frequent on infusion days 3<sup>rd</sup> to 5<sup>th</sup>.

It is remarkable that rash and urticaria persisted even for 72 hours after the last infusion day; therefore, it is important to inform to the patient about this; it will improve patient care.

## Disclosure

López Real A.M. has served as speaker for Biogen Idec, Merck Serono, Genzyme, Novartis and TEVA;

Peña Martínez J. has served as speaker for Sanofi Genzyme, Merck, Bayer, Teva, Biogen Idec, Novartis,

Almirall, Krka and Qualigen; Gonzalez Quintanilla V. has served as speaker for Biogen, Almirall, Merck, Teva, Sanofi-Genzyme, Allergan, MSD and Novartis. He has also participated in clinical trials for AMGEN, Lilly, Sanofi-Genzyme, Allergan y Novartis; Solar Sanchez D.M. has served as consultant for Almirall, Biogen, Bayer, Merck, Novartis, Sanofi-Genzyme, TEVA.

Gonzalez Suarez I. has received grants from Biogen, Novartis, Genzyme;

Pato Pato A. has received grants for clinical research from Biogen, Novartis, Genzyme, Almirall, Bayern;

Amigo Jorrín C. has served as speaker for Sanofi, Novartis, Biogen and Teva;  
 Aguado Valcarcel M. has served as speaker for Biogen, Sanofi Genzyme, TEVA, Novartis, Bayer and MERK-Serono;  
 Alvarez Rodriguez E. has served as speaker or consultant for Sanofi, Biogen and Merck Serono;  
 Arias Gomez, M., has served as advisor for Merck, Biogen-Idec, Genzyme, Roche, Novartis, TEVA, Actelion and Jansen;  
 Lorenzo J.R., has served as speaker and received grants for clinical research from Biogen, Novartis, Genzyme, Almirall, Bayern;  
 Alvarez Fernández L., Lema Devesa D. and Cacabelos Perez, P. nothing to disclose;  
 Oterino Duran A., has served as speaker for Biogen, Almirall, Merck, Teva, Sanofi-Genzyme, Allergan, MSD and Novartis.

### EP1637

#### Effectiveness of fingolimod in Spanish patients with relapsing-remitting multiple sclerosis (RRMS) in daily clinical practice: fingoview study multivariate analysis

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**Background:** Fingolimod has been used in ~204,000 RRMS patients (pts) having a total pt exposure >424,000 pt-years. Analysis of clinical practice data is key to make accurate treatment decisions.

**Objective:** To describe effectiveness variables according to clinical and demographic characteristics in RRMS pts.

**Methods:** Pooled analysis of 2 observational, retrospective, multicentre Spanish studies (MS-Second Line Gate and MS-Next) in ≥18 years RRMS pts treated with fingolimod 0.5mg/day and ≥1 year follow-up after treatment initiation in clinical practice (Nov2014-Dec2015). Regression models were performed to identify potential predictive variables of the number of relapses and Expanded Disability Status Scale (EDSS) score after 1 year of fingolimod treatment using clinical and demographic characteristics at treatment initiation.

**Results:** 988 pts (MS-Next=804, MS-Second Line Gate=184) were analyzed: 69% female, mean age=40 years, post first-line injectable disease-modifying treatment (iDMT)=666, post-natalizumab (NTZ)=252, treatment-naïve=70. The independent predictors of the number of relapses were prior treatment (50% lower in post-iDMT/post-NTZ pts; 65% lower in treatment-naïve/post-NTZ pts), number of relapses in the previous year (32% higher per each additional relapse in the previous year), number of prior treatments (35% lower in pts with ≤1/>1) and number of T2 lesions (34% lower in pts with 9-20/>20 T2 lesions)(p<0.05 all cases). The independent predictors of EDSS score were prior treatment (-0.39 points in post-iDMT/post-NTZ pts; -0.34 points in treatment-naïve/post-NTZ pts), age (+0.008 points per each additional year), EDSS score at treatment

initiation (+0.89 points per each additional EDSS point) and time from RRMS diagnosis (+0.02 points per each additional year)(p<0.05 all cases).

**Conclusions:** The prior treatment, number of relapses in the previous year, number of previous treatments, number of T2 lesions, age, RRMS evolution and EDSS score at treatment initiation should be taken into account before fingolimod treatment initiation since they might predict the clinical disease activity during the first year of treatment.

### Disclosure

S. Martínez Yélamos: Sergio Martínez-Yélamos received honoraria compensation to participate in advisory boards, collaborations as a consultant and scientific communications and received research support, funding for travel and congress expenses from Biogen Idec, Novartis, TEVA, MerckSerono, Genzyme and Almirall

J. Mallada:Ha recibido honorarios de Merck, Bayer, Teva, Sanofi, Novartis, Biogen y Roche

V. Meca-Lallana:Dr. V. Meca Lallana, has received honoraria and travel expenses for scientific meetings and has participated in advisory boards in the past years with: Almirall, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, TEVA and Terumo

J. Meca-Lallana:Nothing to disclosure

M. Martínez:Nothing to disclosure

E. Marzo:Eugenia Marzo has received compensation for travel expenses and speaking honoraria from Biogen Idec, Novartis and Genzyme.

C. Duran: I've received honoraria from Abbvie, Biogen, Novartis, Merck y Sanofi Genzyme

T. Ayuso:T. Ayuso has received compensation for travel expenses, speaking honoraria and consultation fees from Almirall, Biogen, Genzyme, Merck Serono, Novartis and Teva

F. Barrero:Francisco Barrero has received consulting/speaker fees from and advisory board for Bayer HealthCare, Biogen, Genzyme, Merck Serono, Novartis, Roche, Sanofi-Aventis, and Teva, and been involved with clinical trials for Novartis.

R. Romero:Novartis employee

R. Guillen:Novartis employee

J.Ricart:Novartis employee

E. Garcia:Novartis employee

### EP1638

#### Tocopherol-based emulsions as functional vehicles for antigen-specific immunotherapy ameliorate experimental autoimmune encephalomyelitis *in vivo*

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Currently approved therapeutics for Multiple Sclerosis compromise the entire immune system, leading to a susceptibility to severe side effects such as opportunistic infections. Co-delivery applications of antigens with immunomodulatory drugs have shown unique potential to overcome global immunosuppression through their ability to skew immunity with antigen-specificity. Historically, the necessity of a spatially associative vehicle has

been viewed as a setback to co-delivery approaches due to factors such as the immunogenicity of nanoparticles or clinical incompatibility of Freund's adjuvants. Development of a functional vehicle capable of substantially contributing to desired tolerogenic outcomes would be of great value in the advancement of co-delivered antigen-specific immunotherapies (ASITs). In this work, antioxidant tocopherol-based emulsions were selected and evaluated for their functional utility as ASIT vehicles. 4-5 week old SJL/J female mice were induced with experimental autoimmune encephalomyelitis (EAE) and treated with either PBS, tocopherol emulsion alone (ETPGS), or tocopherol emulsion plus 200 nmol PLP<sub>139-151</sub> (ETPGS+PLP, n=3/group) on days 4, 7 and 10. Mice treated with ETPGS alone exhibited a delayed clinical onset, but fully severe disease while ETPGS+PLP-treated mice showed an even further delayed onset with significantly suppressed symptoms. On day 25, splenocytes were harvested and incubated with and without 25µM PLP rechallenge for 120 hours. Following the incubation period, a multiplexed cytokine panel, ELISPOT and flow cytometry were conducted. Significantly increased IL-10 ( $p < 0.01$ ) and IL-4 ( $p < 0.05$ ) were observed in the ETPGS+PLP group over both the PBS vehicle and ETPGS alone, suggesting antigen-specific tolerance. These data, when combined with the clinical effectiveness of ETPGS+PLP show that tocopherol vehicles can serve as potent antigen delivery systems. Further investigation of these formulations may elucidate their utility as functional co-delivery vessels for autoimmune applications.

## Disclosure

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## EP1639

### Acute tumefactive demyelination in a patient on rituximab; a case report

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**Introduction:** Recent clinical trials demonstrating the efficacy of CD20-depleting agents like rituximab, ocrelizumab, and ofatumumab have highlighted the importance of B cells in MS pathogenesis. Although rituximab has extensive use in other autoimmune disorders, relatively limited data exist regarding rituximab real world MS use. We report a case of tumefactive inflammatory demyelination in a relapsing remitting multiple sclerosis (RRMS) patient during rituximab therapy.

**Case report:** A 55 year old man with RRMS, diagnosed in 2013, was started on rituximab 1000mg IV every 6 months after having continued activity despite treatment with IV methylprednisolone, glatiramer acetate, natalizumab, and cyclophosphamide. He remained stable clinically and radiographically for 2.5 years. Six weeks after his fifth cycle, he developed urinary urgency, left hemiplegia and ataxia. Brain MRI demonstrated a large right parietal lobe lesion with incomplete ring enhancement, surrounding edema, and mild mass effect. His cervical and thoracic spine MRI

showed several enhancing lesions. Due to the concern for progressive multifocal leukoencephalopathy, as he was JCV antibody positive, and lymphoma, he was hospitalized. CSF demonstrated signs of active inflammation but was negative for infectious causes including JCV PCR. Flow cytometry revealed no repopulation of B cells. After failing to improve with 5 days of IV methylprednisolone, 5 plasma Exchange resulted in improvement in his clinical symptoms and improvement of his lesion on neuroimaging. Subsequent therapy currently is under consideration - alemtuzumab, adding an immunosuppressant agent to rituximab, or autologous hematopoietic stem cell transplantation.

**Discussion:** Extensive literature review did not yield any previous reports of tumefactive lesion in a rituximab treated patient. Rather, rituximab is sometimes listed as a potential treatment for this condition. This report calls for need for heighten surveillance of MS patient with highly active MS on B cell modulation and raises questions on the best approach going forward.

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## EP1640

### Effectiveness and safety of fingolimod in Spanish relapsing-remitting multiple sclerosis patients in clinical practice (Fingoview study): subanalysis of patients previously treated with first line injectable disease-modifying treatment

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**Background:** Fingolimod is a sphingosine 1-phosphate receptor modulator approved for relapsing-remitting multiple sclerosis (RRMS). Continuous collection and analysis of real world data is key to make accurate treatment decisions.

**Objective:** Fingoview study aimed to describe the effectiveness of fingolimod in Spanish RRMS patients in clinical practice. Here we present the results of the subpopulation previously treated with first line injectable disease-modifying treatment (iDMT).

**Methods:** Fingoview is a pooled analysis of two observational, retrospective and multicentric studies (MS-SECOND LINE GATE + MS-NEXT) including patients  $\geq 18$  years, treated with fingolimod and followed up for  $\geq 12$  months (Nov2014-Dec2015).

**Results:** Fingoview study included 988 patients (MS-Next: 804, MS-2nd-Line GATE: 184). 666 patients were post-iDMT (1 iDMT=382, >1 iDMT=284): 71% female, mean age=40 years,



and mean time from first diagnosis to fingolimod treatment initiation=8 years. The mean annual relapse rate (ARR) of the whole post-iDMT subpopulation decreased by 82%, 88% and 91% at year 1, 2 and 3 after treatment initiation respectively ( $p < 0.0001$  all), with decrease in both 1 iDMT and  $>1$  iDMT subgroups ( $p < 0.0001$  all). The ARR decrease was higher in 1 iDMT than  $>1$  iDMT cohorts (85% vs 78%, 90% vs 84% and 93% vs 87%, years 1, 2 and 3 respectively) with statistically significant difference at year 1 ( $p < 0.05$ ). At year 1, 90% (1 iDMT=91%,  $>1$  iDMT=90%) of patients had stable or improved EDSS that was maintained in 85% (1 iDMT=84%,  $>1$  iDMT=87%) of patients at year 2. There was no significant difference between cohorts. At year 1 and 2, 73% (1 iDMT=69%,  $>1$  iDMT=78%;  $p=0.0696$ ) and 55% (1 iDMT=50%,  $>1$  iDMT=63%;  $p=0.2370$ ) of iDMT patients did not show new/increased T2 lesions respectively, and the mean number of T1 Gd+ lesions decreased by 72% (1 iDMT=74%,  $>1$  iDMT=70%) and 80% (1 iDMT=76%,  $>1$  iDMT=89%) respectively ( $p < 0.0001$ ). At year 1, 83% of 1 iDMT patients and 76% of  $>1$  iDMT were relapse-free ( $p < 0.05$ ). This difference was maintained at year 2 (75% and 67% respectively).

**Conclusions:** Fingolimod is an effective treatment for RRMS patients previously treated with iDMT in clinical practice. For the first 3 years, there was a decrease in the ARR in both 1 iDMT and  $>1$  iDMT cohorts, with a higher reduce in 1 iDMT cohort at year 1. After fingolimod treatment initiation, most than 80% of post-iDMT patients improved or had stable EDSS without differences between 1 iDMT and  $>1$  iDMT cohorts.

## Disclosure

J. Mallada:has received honoraria from Merck, Bayer, Teva, Sanofi, Novartis, Biogen y Roche

J. Meca-Lallana:Nothing to disclosure

M. Martínez:Nothing to disclosure

E. Marzo:Eugenia Marzo has received compensation for travel expenses and speaking honoraria from Biogen Idec, Novartis and Genzyme.

C. Duran: I've received honoraria from Abbvie, Biogen, Novartis, Merck y Sanofi Genzyme

T. Ayuso: T. Ayuso has received compensation for travel expenses, speaking honoraria and consultation fees from Almirall, Biogen, Genzyme, Merck Serono, Novartis and Teva

F. Barrero: Francisco Barrero has received consulting/speaker fees from and advisory board for Bayer HealthCare, Biogen, Genzyme, Merck Serono, Novartis, Roche, Sanofi-Aventis, and Teva, and been involved with clinical trials for Novartis.

V. Meca-Lallana: Dr. V. Meca Lallana, has received honoraria and travel expenses for scientific meetings and has participated in advisory boards in the past years with: Almirall, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, TEVA and Terumo

S. Martínez Yélamos. Sergio Martínez-Yélamos received honoraria compensation to participate in advisory boards, collaborations as a consultant and scientific communications and received research support, funding for travel and congress expenses from Biogen Idec, Novartis, TEVA, MerckSerono, Genyme and Almirall

M.J. Moreno:Novartis employee

I. Salutregui:Novartis employee

J.Ricart:Novartis employee

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## EP1641

### Unexpected systemic reactions following glatiramer acetate 40 mg injections. Experience at 2 multiple sclerosis cCenters

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**Background:** Glatiramer acetate 40 mg 3 times a weeks (GA40) has been approved as an alternative treatment schedule to glatiramer acetate 20 mg daily (GA20). Albeit similar on a weekly basis, a GA40 dose and concentration are twice as high as a GA20 one, and systemic reactions (SR) following each injection might differ.

**Aim:** To investigate unexpected SR (USR) following GA40.

**Methods:** Prospective, observational study performed at 2 tertiary Multiple Sclerosis (MS) Centers between February and May 2017. Consecutive MS patients treated with GA40 for at least 3 months were administered a semi-structured, face to face questionnaire on frequency and characteristics of USR, defined as SR other than chest pain, palpitations, dyspnoea and constriction of the throat following injections. Treating neurologists evaluated USR as mild, moderate or severe. Descriptive statistics were used to describe patients' characteristics and logistic regression was used to evaluate predictors of USR under GA40.

**Results:** 162 patients were included [n=119 (73.4%) females; median (interquartile range, IQR) age 41.5 (35.4-49.3) years; median disease duration 3.4 (1.4-8.9) years; median treatment duration 9(5-12) months; patients previously on GA20 n=96 (59.6%)].Thirty-seven patients on GA40 (22.8%) had  $\geq 1$  USR: of these, 22 (13.5%) had  $\geq 1$  gastrointestinal symptoms (diarrhea, abdominal cramps, nausea/vomiting), 26 (16.0%) fever and/or shivering, and 11 (6.8%) both. A single patient reported abdominal cramps also during previous GA20 exposure. USR were severe in 7(4.3%) patients, and 12(7.4%) patients discontinued GA40 because of SR. Age, gender and previous exposure to GA20 were not related to different risk of USR under GA40.

**Conclusion:** Gastrointestinal symptoms and fever are unexpected SR following GA40 injections and were reported by approximately one quarter of patients. Preliminary data do not support a protective role of previous treatment with GA20.

## Disclosure

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Rossi S acted as an Advisory Board member of Biogen Idec, Bayer Schering, Merck Serono, Teva, Novartis and Genzyme, and received funding for traveling and honoraria for consultancy, speaking or writing from Biogen Idec, Merck Serono, Teva,

Novartis, Bayer Schering, Genzyme, Almirall. She received support for research project by Teva, Merck Serono and Bayer Schering and is involved as principal investigator in clinical trials for Teva, Novartis and Roche.

Mantegazza R acted as an Advisory Board member of Biogarin, received Funding for Travel or Speaker Honoraria from Sanofi-Aventis, Biogarin, Grifols, Teva, Bayer, Alexion, Argenx; he is involved as principal investigator in clinical trials for Alexion, Merck Serono, Hoffmann-La Roche, Teva, Besta-Azienda Ospedaliera San Gerardo, Biogen, Biogarin, Almirall, Novartis, Genzyme Corporation, Catalyst.

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Pareja-Gutierrez L, Camera G, Bellavia G, Bernardini L, Perugini J, Gerardi C have nothing to disclose

Confalonieri P acted as Board member for Biogen-idec and Roche, received support for conference travel from Sanofi-Aventis, Biogen Dompé AG, Merck Serono and Novartis; received support for scientific projects from Merck Serono and Novartis. Torri Clerici V acted as an Advisory Board member of Merck and Genzyme, and received funding for traveling and honoraria for speaking or writing from Biogen, Merck and Almirall. She received support for research project by Almirall.

#### EP1642

##### Real life efficacy and safety of fingolimod: a french southwest and center cohort

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**Background:** Fingolimod is a disease modifying drug used as a second line treatment in very active relapsing remitting multiple sclerosis (MS). It has been used in France since 2011 and we now can provide data about its efficacy and safety in real life.

**Objectives:** This study describes the real life data of efficacy and safety in patients treated with oral Fingolimod from 2011 to 2017 in the cities of Bordeaux, Tours, Toulouse and the Auvergne region.

**Methods:** We retrospectively collected data from the EDMUS database and from patient's medical files in the universities hospitals of Bordeaux, Toulouse, Tours and Clermont-Ferrand, general hospitals and neurologists in Auvergne.

We focused on the population characteristics, efficacy (Annualized Relapse Rate (ARR), MRI and the Expanded Disability Status Scale (EDSS) evolution) and safety of Fingolimod.

**Results:** Baseline characteristics of the 432 patients : mean age  $39.9 \pm 10$  years; sex ratio women/men 3.8; duration of MS when Fingolimod is introduced  $10.28 \pm 7.8$  years, numbers of relapses during the past two years  $1.5 \pm 1.3$ ; ARR during the past two years 0.76; mean EDSS 2.68 (0-8.5); 29% MRI contrast enhancing.

6.25% received Fingolimod as a first line treatment, 36.8% after a natalizumab cure. ARR was decreased by 67.1% after a two years following. Mean EDSS was slightly increased after 1 year of treatment (2,7) and stable after 2 years (2,6). 78.7% patients were free from MRI progression the first year.

27% of patients interrupted the treatment, mainly because of a lack of efficacy or severe adverse events.

Severe infections were the reason for the interruption for 10 patients.

The others adverse events for which Fingolimod was stopped are: 4 atrioventricular block during the first introduction, 16 severe lymphopenia, 7 hepatitis, 4 macular oedema, 3 severe asthenia, 3 cancers (1 tongue epidermoid carcinoma, one basocellular carcinoma, one uterine cancer), 2 headaches, 3 vomitings/diarrhea, 1 interstitial pneumoniae, 1 autoimmune hemolytic anemia. We did not report any case of progressive multifocal leukoencephalopathy in our cohort.

**Conclusions:** Fingolimod shows efficacy on the ARR with an important reduction during the first two years. In our cohort, most of the patients were also free from disability progression during these two years.

Fingolimod is overall well tolerated, even if it was stopped because of severe adverse events in 12.5% of patients.

#### Disclosure

Roux: nothing to disclose

Simeoni: nothing to disclose

Thomas: nothing to disclose

Brassat: nothing to disclose

Guennoc: nothing to disclose

Brochet: nothing to disclose

Clavelou: nothing to disclose

#### EP1643

##### The efficacy and safety of the biosimilar interferon beta-1a Teberif® in patients with relapsing-remitting multiple sclerosis: data from a comparative international multicenter double-blind placebo-controlled randomized phase III study

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Petersburg, Russian Federation

**Background:** Biosimilars of interferon beta-1a are being introduced in clinical practice in patients with relapsing-remitting multiple sclerosis (RRS).

**Objectives:** To demonstrate the equivalence of the biosimilar interferon beta-1a Teberif® and the originator Rebif® in the treatment of RRS.

**Materials and methods:** The study involved 163 patients with RRS, duration of the disease  $\geq 12$  months and EDSS score of 0-5.5. Randomization: 1:1:1 - Group 1 (Teberif®), Group 2 (Rebif®) for 52 weeks and Group 3 (placebo) for 16 weeks then Teberif® for 1 year. 137 patients completed the study. The primary end point was assessment of MRI outcomes - CUA (combined unique active lesions).

**Results:** After 16 weeks of the study, Teberif® and Rebif® showed equivalent efficacy and were superior to placebo.

Groups 1 and 2 did not differ by the number of CUA ( $p=0.898$ ). The pair-wise comparison of groups 1 and 2 with placebo showed statistically significant differences ( $p=0.038$  and  $p=0.024$  respectively).

After one year of the treatment, CUA in Groups 1 and 2 (mean  $\pm$  standard deviation) was  $0.727 \pm 1.042$  and  $0.652 \pm 1.059$  ( $p = 0.735$ ). The percentage of patients without Gd+ lesions was 75.00% and 80.43% (Groups 1 and 2, respectively) ( $p=0.718$ ). Similar data (without significant differences between the groups) were obtained for all other MRI outcomes. During the year of the treatment, most patients did not have relapses (89.1% vs. 91.7%, Groups 1 and 2,  $p=0.737$ ). Baseline EDSS scores at screening were 2.5 in both groups, while after one year of therapy - 2.0 ( $p=0.546$ ).

Groups did not differ by the frequency, nature, and severity of adverse events. No serious adverse events were reported during the entire period. The drugs had similar immunogenicity; they rarely induced the development of neutralizing antibodies (in 10 and 9 patients in Groups 1 and 2,  $p=0.928$ ). The final assessment of immunogenicity will be performed after 2 years of treatment.

Patients who received placebo during the first 16 weeks completed their one-year course of treatment with Teberif®. In this Group mean values of CUA before the treatment were  $3.286 \pm 5.216$ , after one year of the treatment -  $1.048 \pm 2.083$  ( $p=0.0001$ ). The percentage of patients without contrast-enhancing lesions was 80.95%, without confirmed relapses - 90.74%.

**Conclusions:** Biosimilar Teberif® showed the equivalence to Rebif® by all parameters of efficacy, safety, and immunogenicity in patients with RRS.

## Disclosure

This study was sponsored by JSC Biocad.

C. Tursunova, A. Zinkina-Orikhan are employees for Biocad company.

## EP1644

### Real world data on teriflunomide and dimethyl fumarate treatment of multiple sclerosis

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**Background:** Multiple Sclerosis (MS) is characterized by inflammatory demyelinating lesions in the central nervous system and a heterogeneous clinical course. No curative treatment exists, but various disease modifying therapies are available. Teriflunomide (Aubagio®) and dimethyl fumarate (Tecfidera®) are two oral first-line therapies that since 2013/2014 have been approved for the treatment of MS in Norway. Oral medications have several advantages compared to injection therapies, especially side effects

related to injections. However, it is still unknown if there are differences in efficacy and side effects influencing compliance and adherence to therapy between these oral agents. We have therefore examined real world data of teriflunomide and dimethyl fumarate treatment in a population of Norwegian MS patients.

**Methods:** We examined the 237 MS patients at Haukeland University Hospital, Western Norway, who were treated with either dimethylfumarate (N=109) or teriflunomide (N=130) during May 1<sup>st</sup> 2014 to November 1<sup>st</sup> 2016. We recorded the frequency of attacks before, during and after the use of the oral medication, side effects, duration of the treatment and the reason for switching therapy among several other factors. We performed a Kaplan Mayer analyses of time to switching therapy during the first 52 weeks of therapy.

**Results:** The mean observation period on teriflunomide therapy was 57 weeks (range: 1 - 154), and 71 weeks (range: 1 -142) on dimethylfumarate. A total of 74% of the patients receiving dimethyl fumarate experienced side effects, while only 44% of the patients using teriflunomide did. Flushing and gastrointestinal side effects were most frequent in dimethyl fumarate treated patients, and hair thinning and gastrointestinal side effects most frequent in teriflunomide treated patient. A total of 29 (22 %) patients that received teriflunomide, and 35 (32 %) patients that received dimethyl fumarate switched therapy during the observation period. Kaplan Mayer analyses of time to switching therapy during the first 52 weeks showed that patients on dimethyl fumarate had a shorter time to switching therapy compared to those that received teriflunomide ( $p=0.07$ ).

**Conclusion:** Side effects were more frequent in patients that received dimethyl fumarate compared teriflunomide. Although not statistically significant different, patients on dimethyl fumarate therapy had a shorter time to switching therapy compared to those that received teriflunomide.

## Disclosure

Hilde Norborg reports no disclosures

Philipp Strauss reports no disclosures

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## EP1645

### Comparing efficacy between natalizumab and fingolimod: radiological findings from BEST-MS study

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**Objective:** To compare efficacy between natalizumab (NTZ) and fingolimod (FTY) in active relapsing remitting multiple sclerosis (RRMS)



**Methods:** BEST-MS was a French multicentric study (ClinicalTrials.gov Identifier: NCT01981161) with prospective data collection involving patients with active RRMS who started either NTZ or FTY. Treatment choice was patient's and physician's discretion. Last patient was recruited by September 2016. Efficacy was assessed by clinical (EDSS, relapses) and MRI parameters (number of new T2 lesions, number of gadolinium enhancing lesions) after 12 months of therapy, and compared between treatment groups. We present data about MRI findings.

**Results:** 224 patients were included in 10 MS centers (NTZ : 111; FTY : 113). Sex ratio was 3.15, mean age was 30 [12-62]. Mean disease duration was 6 years. Baseline EDSS was 2.4 [0-6.5] and mean number of relapses during the 12 months preceding initiation of treatment was 1.4 [0-3]. To date, we collected both initial and 1-year MRI data for 66 patients.

Comparison between treatment groups showed that NTZ patients had a shorter disease duration (3.4 vs 7.4 months;  $p < 0.05$ ) and a higher relapse rate before treatment initiation (1.6 vs 1.1;  $p < 0.05$ ). Regarding MRI, there was no significant difference between groups at baseline.

After 12 months, mean number of new T2 lesions was 0.45 [0-5], without any difference between treatment groups. Mean number of gadolinium enhancing lesions was 0.1 [0-3]. There was a significant lower number of gadolinium enhancing lesions in patients treated with NTZ (0.06 vs 0.18;  $p < 0.05$ ).

**Discussion:** Regarding MRI parameters, NTZ seems to be more effective than FTY in reducing the number of gadolinium enhancing lesions.

Further analysis will be performed to compare clinical efficacy between treatment groups

**Conclusion:** We present MRI results of BEST-MS study. Results suggest a higher efficacy of NTZ compared to FTY on radiological parameters.

## Disclosure

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## EP1646

### A novel case of autoimmune myositis after alemtuzumab therapy for multiple sclerosis

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**Objectives:** We describe the case of a 44-year-old female who developed a previously unreported, corticosteroid-responsive, autoimmune, non-necrotising myositis after receiving alemtuzumab for relapsing remitting multiple sclerosis (RRMS).

**Case report:** A 44-year-old female with a 13-year history of RRMS was treated with alemtuzumab without any immediate complications in November of 2015. Her baseline EDSS at the time of treatment was 2.0, with MRI showing widespread demyelination affecting the deep white matter of the brain, optic nerves and spinal cord. Seven months later she developed myalgia affecting the arms and legs in a proximal distribution. Clinical assessment and MRI excluded progression of multiple sclerosis (MS). Blood tests showed a grossly elevated creatine-phosphokinase level (CK) of 11015 U/L ( $< 211$  U/L). Hepatic transaminase levels were also elevated at 322 U/L and 129 U/L ( $< 30$  U/L) for AST and ALT respectively.

Electromyography demonstrated myopathic units in keeping with a mild generalized non-necrotizing process. A muscle biopsy was obtained from the left quadriceps. Occasional lymphocytes were seen but there was neither necrosis nor a significant inflammatory infiltrate. Rare fibers were positive for C5b9, the terminal component of complement.

Corticosteroid therapy was started and weaned to 5mg over a 3-month period. The patient's symptoms resolved completely and correlated with decreases in serum CK levels.

**Discussion and conclusion:** Secondary autoimmunity affecting the thyroid, platelets and rarely the kidneys is well described following immune reconstitution after alemtuzumab. Each of these complications involves antibody-dependent immunity. This case of myositis also appears to be autoimmune and involves humoral immunity. A cellular infiltrate could not be shown on muscle biopsy, but complement activation was present and steroids were highly effective. In the absence of histopathological evidence of T-cells, macrophages or necrosis, we propose this form of myositis may be a unique entity and term the condition, pauci-immune myositis. This case highlights the importance of reporting novel

adverse events with emerging immune therapies for MS. Further research is required to understand the mechanisms underlying secondary autoimmunity after alemtuzumab treatment.

### Disclosure

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### EP1647

#### The Alemtuzumab MS Safety Systems (AMS3) study: clinical outcomes

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**Background:** The AMS3 study tracked the development of a system to improve pathology monitoring and alerting of abnormalities in patients treated with alemtuzumab for MS.

**Aims:** To report the clinical & MRI outcomes of 10 patients with very active relapsing remitting MS treated with alemtuzumab and followed for 2 years.

**Methods:** Ten patients selected by rank order of need from 30 nominated by neurologists from Australia, with highly active MS and failure or unsuitability for other therapies. Clinical and MRI measures are reported given the unique severe nature of this cohort. The endpoints of the study are reported separately.

**Results:** At baseline (BL), mean age = 36 (24 - 57), disease duration = 5.3Y (2 - 10), relapses prior 12 months = 2.3 (1-5), EDSS = 3.05 (2 - 4). Mean prior MS therapies = 2.9 (1-6 - all had prior natalizumab, 9 JC+). The reason for alemtuzumab given was: relapse on fingolimod (6) or DMF(2); relapse on natalizumab, JC- (1); relapse while pregnant, JC+ (1).

During the study, 3/10 patients had relapses. One patient had 4, without change in exam or MRI. Two other patients had 2 relapses each, with new features and MRI lesions. The annualised relapse rate declined to 0.4 (from 2.9), an 86% ARR reduction. The mean EDSS declined from BL=3.05, to Y1=2.25, and Y2=2.22. Seven patients had confirmed disability improvement, 2 unchanged, 1 confirmed disability worsening. That patient had cord relapses with pial spinal cord enhancement and cerebral Gd+ lesions unchanged over 2 years suggesting a non-MS disease such as sarcoid.

On completion, mean MRI-T2-hyperintense lesion volume increased 3.6% BL-Y1, then declined -3.1% Y1 - Y2. Atrophy (SIENA): average -0.97% (SD 0.68%) brain atrophy BL-Y1 and -0.29% (SD 0.53%) Y1-Y2. Both suggest a contribution of active disease and subsequent pseudoatrophy in the first year with brain volume changes approximately normal in the second year. The mean Gd lesion number at entry was 9.2 (0-26), Y1 1.9 (0-13), Y2 0.11 (0-1). Conversion of enhancing lesions to T1-black holes: 4

patients at BL (n lesions = 1,1,2,2), no Y1 Gd lesions converted to black holes.

**Conclusions:** Alemtuzumab is a highly effective treatment for MS, even in a highly active cohort with considerably more pre-treatment than patients in the pivotal trials. Careful review of the diagnosis is needed in atypical cases before alemtuzumab treatment. Marked improvement in relapse rates, new Gd lesions, and second year brain atrophy occurred.

### Disclosure

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### Disclosures

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D. Gahan is a shareholder in Medical Safety Systems P/L Australia, owner of the RiskMx™ system.

F. Fitzgerald is an employee of Medical Safety Systems P/L Australia, owner of the RiskMx™ system.

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D. Erickson reports no disclosures

## EP1648

**Observational study of the factors leading to the switch to fingolimod after first-line therapy in patients with relapsing-remitting multiple sclerosis in France: interim analysis ESGILE study**

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**Background:** Fingolimod, a sphingosine 1-phosphate receptor modulator, was the first approved oral disease-modifying therapy (DMT) in patients with multiple sclerosis (MS). In France, it is indicated in patients with high disease activity despite previous treatment with at least one DMT or patients with rapidly evolving severe relapsing remitting MS (RRMS). Retrospective database studies of patients with MS disease have demonstrated the superiority of switching to more efficacious therapy such as fingolimod compared to cycling between first-line DMTs. However, factors supporting the switch decision to fingolimod are not yet understood.

**Objective:** The objective of this study is to describe the factors leading to the switch to fingolimod after initial DMT in patients in clinical practice and to follow up with clinicians and patients on their treatment satisfaction after 1 year.

**Methods:** ESGILE is an observational, non-interventional, multicentric, 12-month, prospective study conducted in France in patients with RRMS. Included patients should have started fingolimod no longer than 4 weeks before baseline visit in line with its approved indication. Visits were scheduled at 6 and 12 months. This interim analysis describes the baseline characteristics of the patient population and the reasons for switching to fingolimod as a second-line treatment. Other outcomes will include clinical and patient global impression changes, and quality-of-life questionnaire (ACCEPT).

**Results:** Between November 2015 and March 2016, 35 centers included 87 patients with mean age of 40.3 years, 79.3% females, MS diagnosis of 5.8 ± 6.2 years, Expanded Disability Status Scale (EDSS) average score of 2.1 ± 1.3. The main reason for therapeutic change was the disease progression (74.7%), followed by administration modalities (34.5%), patient choice (14.9%), and tolerability (6.9%).

**Conclusion:** The change in treatment is mainly motivated by the progression of disease activity. This study also revealed a high occurrence for therapeutic change from other DMT to fingolimod that is linked to the administration modalities.

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 Karin Rerat, Mohamed Meite, Isabelle Chouette: Are Novartis employees

## EP1649

**Efficacy and safety of daclizumab beta in patients with relapsing-remitting MS switching from natalizumab: rationale and study design of the phase 3b SUSTAIN study**

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**Background:** Treatment sequencing of disease-modifying therapies (DMTs) is a key consideration in the management of relapsing MS. Natalizumab is a highly effective DMT. However, some patients stop treatment with natalizumab because of reasons other than efficacy, primarily due to concerns about the risk of developing progressive multifocal leukoencephalopathy (PML). Identifying DMTs that can be effectively and safely used in the post-natalizumab treatment setting is a key unmet medical need. Daclizumab beta (DAC BETA) is a once monthly subcutaneous (SC) DMT for relapsing MS that offers high efficacy and a manageable safety profile through routine monitoring with no increased risk of opportunistic infections versus placebo or IM interferon beta-1a, and no cases of PML to date.

**Objectives:** To evaluate the efficacy and safety of DAC BETA in subjects who switch from natalizumab to DAC BETA.

**Methods:** SUSTAIN (NCT02881567) is a 12-month (mo), open-label, multicentre phase 3b study. Eligible adult relapsing-remitting MS (RRMS) subjects have: EDSS score 0-5.5; been treated with natalizumab for ≥12 months prior to screening without missing ≥2 consecutive doses; no relapse, increase in EDSS, Gd<sup>+</sup> or new/newly enlarging T2 lesions in the last ≥6 months; and been enrolled within 28(+3) days of last natalizumab dose. At the end of the 28(+3) day period, subjects receive DAC BETA 150mg once monthly SC using a pre-filled pen during 12 mo of follow up. Study assessments occur at enrolment, baseline, and 1, 3, 4, 6, 9 and 12 mo with a safety follow-up visit 4 (EU sites) or 6 (US/Canada sites) mo after the last dose; brain MRI scans are performed at enrolment and 1, 4, 6 and 12 mo (all time points: pre-contrast T1, T2, PD, FLAIR; enrolment and 1, 4 and 6 mo: DWI; enrolment and 6 and 12 mo: post-contrast T1). The primary endpoint is the proportion of subjects relapse free at 6 mo; secondary endpoints include: incidence of AEs/serious AEs, proportion of subjects relapse free and annualised relapse rate at 12 mo; number of new Gd<sup>+</sup>, new T1 hypointense, and new/newly enlarging T2



hyperintense lesions at 6 and 12 mo; and rate of permanent discontinuation of DAC BETA at 12 mo.

**Results:** SUSTAIN is expected to enrol ~100 subjects. Enrolment is ongoing. Estimated study completion is early 2019.

**Conclusions:** Results from SUSTAIN will provide information about the efficacy and safety of DAC BETA in RRMS patients initiating this therapy after discontinuation of treatment with natalizumab.

## Disclosure

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## EP1650

### Real-world treatment satisfaction with teriflunomide: results from the European cohort of the phase 4 Teri-PRO study

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**Background:** Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS. The Teri-PRO study (NCT01895335) previously reported high levels of treatment satisfaction with teriflunomide in routine clinical practice. The global nature of Teri-PRO allows for an assessment of the influence of different treatment practices on outcomes among participating countries.

**Objective:** To report treatment satisfaction with teriflunomide in the European cohort of the Teri-PRO study.

**Methods:** Patients in Europe received teriflunomide 14 mg, according to local labelling. The primary outcome was Global Satisfaction with treatment at Week (W) 48, measured using the Treatment Satisfaction Questionnaire for Medication (TSQM, version 1.4). TSQM scores were measured at baseline (patients switching from a prior disease-modifying therapy [DMT] within the previous 6 months), and at W4 and W48/end of treatment (all patients). In this post hoc analysis, patients in Europe were stratified into 4 regions: Nordics (Norway, Finland, and Sweden), Southern Europe (SE; Greece, Italy, and Spain), Central Europe (CE; France, Belgium, Austria, and Germany), and the UK.

**Results:** Mean (SD) age (years) was 43.8 (9.3) in the Nordics (n=63), 41.7 (9.3) in SE (n=121), 42.5 (10.6) in CE (n=205), and 45.3 (9.1) in the UK (n=44); baseline EDSS score was 1.8 (1.4), 2.3 (1.5), 2.1 (1.3), and 3.2 (1.9), respectively. TSQM Global Satisfaction remained high over the study period in all regions (mean [95% CI]; Nordics: W4 73.1 [68.0,78.1], W48 71.9 [65.6,78.2]; SE: W4, 68.7 [65.6,71.7], W48 64.2 [59.8,68.5]; CE: W4 72.2 [69.2,75.3], W48 66.8 [63.1,70.6]; UK: W4 80.4 [74.5,86.4], W48 76.2 [68.1,84.2]). In patients switching from another DMT, Global Satisfaction significantly improved from baseline to W4 (Nordics: baseline 57.3 [50.5,64.2], W4 75.7 [70.1,81.2],  $P=0.0192$ ; SE: baseline 52.9 [47.7,58.0], W4 72.0 [68.3,75.6],  $P<0.0001$ ; CE: baseline 56.7 [51.9,61.5], W4 75.4 [71.7,79.0],  $P<0.0001$ ; UK: baseline 43.5 [31.0,55.9], W4 80.0 [71.0,89.1],  $P=0.0003$ ) and remained high to W48 (Nordics: W48 75.3 [68.2,82.3],  $P=0.0840$  vs baseline; SE: W48 64.2 [58.9,69.4],  $P=0.0335$ ; CE: W48 69.9 [65.2,74.6],  $P<0.0001$ ; UK: W48 72.2 [59.1,85.3],  $P=0.0209$ ).

**Conclusions:** High levels of treatment satisfaction were observed in Europe regardless of region, including significant improvements in patients switching from another DMT. These results are consistent with the full study population.

## Disclosure

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**PV:** Honoraria, consulting fees (Almirall, Bayer, Biogen Idec, Genzyme/Sanofi, GSK, Merck Serono, Novartis, Teva); research support (Bayer, Biogen Idec, Genzyme/Sanofi, Merck Serono).

**JML:** Consulting fees (Almirall, Biogen Idec, Merck Serono, Novartis, Sanofi, Teva).

**EM:** Consulting fees (Teva), travel grants (Novartis).

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**HK:** Consulting fees and travel grants (Biogen, Genzyme, Merck, Novartis, Teva).

**GC:** Compensation in past year for consulting services and/or speaking activities (Almirall, Biogen, Celgene, Excemed, Forward Pharma, Genzyme, Merck, Novartis, Receptos, Roche, Sanofi, Teva); fees from non-CME services (Almirall, Bayer, Biogen, Excemed, Genzyme, Merck Serono, Novartis, Receptos, Sanofi, SSIF, Teva).

**RJ:** Consulting fees (Almirall, Biogen, Genzyme/Sanofi, Merck, Novartis).

**WR:** Nothing to disclose.

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**PR and EP:** Employees of Sanofi Genzyme.

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### EP1651

**Surface charge distribution, an attribute linked with immunogenicity of nanoparticles, is different for follow-on glatiramer acetate products approved in EU, Russia, Latin America and USA compared with Copaxone**

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**Background and objectives:** Given its structural and compositional complexity, Copaxone (Teva, glatiramer acetate) cannot be fully characterized using current state-of-the-art methodologies. As studies indicate a correlation between surface charge and immunogenicity of polypeptides (Foged C Int J Pharm 2005; Bhattacharjee S Part Fibre Toxicol 2010; Fromen CA Nanomedicine 2016), Teva employed a gold standard for charge-sensitive antibody analysis, Cation Exchange Chromatography (CEX), to further assess the surface charge attributes of Copaxone and compare them to follow-on glatiramer acetate (FOGA) products marketed in Europe, the USA, Russia and Latin America.

**Methods:** CEX is based on a non-destructive separation of polypeptide mixtures into subgroups according to their average overall surface charge. Copaxone samples consistently comprise of three subpopulations represented by distinct peaks on CEX chromatograms: weak negatively charged, weak positively charged, and strong positively charged polypeptide subpopulations.

**Results:** The charge distribution for the marketed batches of FOGAs differed from that of Copaxone batches in terms of the distribution of the typical three distinct subpopulations. Charge distribution values of Polimunol (Argentina), Axoglatiran (Russia), and Synthon's European FOGA (Europe) were outside the Copaxone range of values for the negatively charged subpopulation and weak positively charged subpopulation. For the strongly positively charged distribution, all of Polimunol and Axoglatiran

batches and 4 of 6 batches of the Synthon European product were above the Copaxone range. Glatopa batches demonstrated inconsistent results with the negative subpopulation varying from higher to significantly lower values than Copaxone thresholds; weak positive distributions were lower than Copaxone in all batches; and strongly positive subpopulation were higher than the Copaxone range in six out of eight batches.

**Conclusion:** All tested FOGA products demonstrated varying degrees of altered surface charge relative to Copaxone. Since this hypothesis has already been confirmed for Polimunol and Glatopa, showing robust differences in gene expression profiles of immune-mediated inflammatory pathways (Laifenfeld Ectrims 2016; Kolitz Ectrims 2016, respectively), further investigation of FOGA-induced immunogenicity is warranted.

### Disclosure

All authors are employees of Teva Pharmaceutical Industries, the sponsor of the research conducted in this report.

### EP1652

**Physicochemical and biological characterization of the European follow-on glatiramer acetate product as compared to copaxone**

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**Objective:** Copaxone (Teva, glatiramer acetate), has provided a safe and effective treatment option for multiple sclerosis for 20+ years. The European regulatory assessment of follow-on-glatiramer acetate (FOGA) relied on establishing similarity rather than sameness of the active substance, and followed a biosimilar type approach. Copaxone release tests, high resolution physicochemical tests and biological assays were employed to evaluate compositional characteristics and their associated and functional ramifications, when comparing European FOGA relative to Copaxone specifications or inherent variability ranges.

**Methods:** The characterization methods included molecular weight distribution (MWD), Coomassie Brilliant Blue G-250 (CBBG), Viscotek TDAmass, cation exchange chromatography (CEX), Atomic Force microscopy (AFM), 2D-RPLC MALLS, cell-based potency, cytotoxicity, and ELISA assays using monoclonal (MAb) and polyclonal (PAb) antibodies for bio-recognition of glatiramer acetate.

**Results:** The FOGA batches (n=6) were within the Copaxone specification or variability ranges for the following methods; MWD, CBBG, AFM, 2D-RPLC MALLS, potency, and bio-recognition by MAb and PAb antibodies. Several compositional attributes were consistently different between the FOGA and Copaxone, including molecular size, hydrodynamic radius, and intrinsic viscosity (Viscotek). Charge distributions of the FOGA batches were outside the Copaxone value range for negatively charged and weak positively charged subpopulations, and for 4 out of 6 batches, also for the strongly positively charged subpopulation (CEX). Biological tests showed distinctly higher potency of

all FOGA batches as compared to Copaxone although results were within the potency specification range. Furthermore, a third of the FOGA batches demonstrated higher *in vitro* cytotoxicity activity than the established Copaxone specification range.

**Conclusion:** When applying state-of-the-art methodologies, consistent differences were observed in compositional characteristics of the European FOGA product. Altered surface charge distribution has previously been associated with cytotoxicity and potency alterations (Bhattacharjee et al. 2010; Fromen et al. 2016) and was confirmed herein experimentally. Associated immunogenicity risks warrant investigation.

## Disclosure

All authors are employees of Teva Pharmaceutical Industries who sponsored the research described in this report

## EP1653

### A prospective evaluation of fingolimod MRI outcomes in Puerto Rico Hispanic population

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**Background:** Fingolimod (FTY) is a well-known and effective Sphingosine-1-phosphatase receptor immunomodulator to treat patients with Multiple Sclerosis (MS). Hispanic MS patients comprise less than 3% of the patient population in major clinical trials. Therefore, clinical data regarding treatment efficacy in controlling disease burden via MRI parameters is vastly limited.

**Aim:** FTY efficacy in Hispanic MS patients by MRI outcomes on T1 gadolinium enhancing lesions (GAD+), new/enlarging T2 lesions (T2), T1 hypointense lesions (T1BH).

**Methods:** Single-center, open label, non-comparative, 2-year observational longitudinal follow-up study from 2012-2014. All patients were diagnosed by the 2010 McDonald Criteria and treated by a MS specialized neurologist at the largest nationally accredited MS center in Puerto Rico (PR). All patients had pre and post treatment imaging at a designated center with 1.5T MR and interpreted by a Neuroradiologist trained in MS imaging protocol. Patients were imaged at 1 year intervals. IRB approval and informed consent was obtained.

**Results:** 150 patients were enrolled and 81.5% (119) patients completed the 2 year trial. Females represent 78.1%(114) of original patient population. Mean age of diagnosis was 40.8 ± 10.9 and mean duration of disease (years) 6.6 ± 6.0. 13%(19) of the patient population was treatment naive. 2.6%(4) of patient population were lost to follow up and 18.4%(27) discontinued treatment. Reasons for discontinuation include 11.1%(3) experienced adverse events (AE), 2 macular edema and 1 arrhythmia, and 25.9%(7) were non-responders. At baseline, 22%(31) of patients had GAD+ lesions. At 1 year and 2 years, 8.6%(9) and 5.2%(4) of patients had T1GAD+ lesions, respectively. This means at year 1 and year 2 there was a 91.3% and 94.5% reduction in T1GAD+ lesions. At baseline, 24.5%(34)

had T2 lesions. At 1 year and 2 years, 78.9%(82) and 77.9%(60) of patients showed a reduction of T2 lesions. At baseline, 44.6%(62) of patients had T1BH. Of the T1BH negative patients, at 1 and 2 year follow up, 3%(3) and 0% (0) developed T1BH lesions, respectively.

**Conclusion:** FTY showed a great response in MRI outcomes in PR Hispanic population. Specifically, in patients with active disease. The authors recommend the inclusion of Hispanic population in future clinical trials.

## Disclosure

Angel Chinae: consultant and speaker for Novartis, BIOGEN, TEVA, SANOFI, ACCORDA.

The remaining authors have no other disclosure.

## EP1654

### Teriflunomide in Real World Practice: further benefit in previously treated multiple sclerosis patients. A multicenter, 2 years retrospective study

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**Introduction:** Teriflunomide (TER) has been effective and secure in multiple sclerosis (MS) clinical trials (CTs) recruiting mainly naïve patients. Some real-world evidence is now available suggesting TER is even efficient for patients who differ mostly from CTs, but the follow-up is still too short.

**Objective:** To analyze the efficacy and tolerability of TER with respect to previous disease modifying therapy (DMT).

**Methods:** We retrospectively recorded clinical and radiological data from 255 patients who underwent teriflunomide. Comparisons were made using t test or sign test for numerical variables, and  $\chi^2$  for categorical variables.

**Results:** A total of 255 patients' records (mean of age=45.27±11.5y) who were on treatment (13.1±6.7mo) from december 2014 to march 2017; 184 females) were reviewed. MS types (n=242) were classified as relapsing-remitting, and 13 as progressive forms (mean disease duration=10.92±8.5y). Most (n=171) were on at least one DMF (43.13% from IF), 37 patients switched to TER because of inefficacy, and 134 for intolerance. Annual relapse rate (ARR) was significantly reduced in 191 patients completing at least 1y on treatment (basal ARR=0.950±0.7; 1y ARR=0.246±0.5; p<0.0001), 2<sup>nd</sup>y ARR=0.5±0.6 (n=37; p=0.006). Multivariate regression, adjusted for sex, and age, disclosed no differences for TER response after 12 mo by previous treatment (absolute ARR reduction=0.588±0.09 for naïve patients, and 0.673±0.1 for switchers). After 1y, basal EDSS (mean=1.992±1.4) remained stable in 73.71% (p=0.093), and in 84.12% in the 2<sup>nd</sup>y (p=0.028). MRI scans (basal n=236; 1<sup>st</sup>y n=77) showed no new T2 lesions in



61.44%. Number of Gd+T1 lesions decreased after 1y ( $p=0.066$ ). No serious adverse events were recorded.

**Conclusions:** In real word, most patients switched from other therapies to TER, and they were older. than in CTs. Even in this scenario, TER was clinical and radiologically effective. We observed a further potential benefit for those switching from other therapies, mainly IFB and GA, independently of the reason for switching.

### Disclosure

Villafani J has received honoraria for speaking from Biogen Inc., TEVA, Novartis, Merck, Sanofi Genzyme, Roche.

Peña J, has received honoraria for speaking from Biogen Inc., TEVA, Novartis, Merck, Sanofi Genzyme.

Oliva P has received honoraria from Biogen Inc., TEVA, Novartis, Merck, Sanofi Genzyme, Roche

Ares A has received honoraria from Biogen Inc., TEVA, Novartis, Merck, Sanofi Genzyme.

Hernandez L has received honoraria from Biogen Inc., TEVA, Novartis, Merck, Sanofi Genzyme.

Perez D has received honoraria from Biogen Inc., TEVA, Novartis, Merck, Sanofi Genzyme.

Solar DM has received honoraria from Biogen Inc., TEVA, Novartis, Merck, Sanofi Genzyme, Roche

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Lara L has nothing to disclose

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### EP1655

#### Efficacy and safety of natalizumab extended interval dosing

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**Objective:** Natalizumab is highly effective in MS but carries the risk of progressive multifocal leukoencephalopathy (PML). It is postulated that extending the dosing interval from 4 to 5-8 weeks might decrease this risk by decreasing the  $\alpha 4$  integrin saturation on the surface of mononuclear cells. The aim of this study was to assess the effect of extended interval dosing (EID) on the therapeutic efficacy of natalizumab.

**Methods:** We reviewed all patients treated in our MS center with natalizumab for at least 6 months using EID. A total of 55 patients were shifted after an initial treatment period at standard interval dosing (SID) to an EID ranging from 5 to 8 weeks. All patient had a baseline MRI before initiating therapy and a follow-up MRI every 6 months thereafter.

**Results:** The mean treatment duration on SID and EID was  $16.7 \pm 13.0$  and  $9.1 \pm 6.4$  months respectively. The mean age of our patients was  $35.9 \pm 11.7$  years, mean disease duration  $5.4 \pm 6.4$  years,

79.5% were females, and 94.5% had relapsing remitting MS as opposed to 5.5% with secondary progressive MS. Before initiating therapy, annualized relapse rate (ARR) was 0.83, mean EDSS  $2.52 \pm 1.5$ , and 63.6% of patients were JCV antibody positive (Antibody index  $\leq 0.9$  in 72.5% and  $\geq 1.5$  in 25.5% of cases). By the end of SID and EID treatment 92.7% and 93.3% of patients were free of relapses ( $P=NS$ ) and the ARR decreased to 0.05 and 0.06 respectively ( $P=NS$ ). The mean EDSS at the end of SID and EID periods was  $1.7 \pm 1.4$  and  $1.8 \pm 1.3$  respectively ( $P=NS$ ). A total of 72.7% and 92.7% of patients were free of any new T2 or enhancing lesions on MRI during the SID and EID periods respectively ( $P=0.011$ ). It is of note that in the SID group the baseline MRI was performed before starting natalizumab. The overall incidence of adverse events was 51% vs 31% during SID and EID periods respectively. Specifically the rate of infections was higher during SID compared to EID (42% vs 20%). There were no cases of PML.

**Conclusion:** In patients treated with natalizumab, shifting from SID to EID has no negative effect on efficacy as evidenced by relapse rate, disability progression and MRI activity. The EID regimen is associated with a lower rate of infections and might potentially decrease the risk of PML.

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Samia J. Khoury: nothing to disclose

Bassem I. Yamout: nothing to disclose

### EP1656

#### A case of Legionnaires' disease in a patient on dimethyl fumarate therapy for relapsing-remitting multiple sclerosis

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**Objective:** We present a case of Legionnaires' disease in a patient on dimethyl fumarate (DMF) with lymphopenia.

**Background:** Lymphopenia is a well-established consequence of DMF therapy. A myriad of infections have been reported in lymphopenic patients on DMF including respiratory, urinary tract, herpes virus, and gastrointestinal infections. Special attention has been paid to the risk of progressive multifocal leukoencephalopathy in patients on DMF with very low or rapidly dropping lymphocyte counts. To our knowledge there are no reported cases of Legionnaires' disease in a patient on DMF.

**Discussion:** The patient was diagnosed with relapsing-remitting multiple sclerosis (RRMS) in September 2013 after an episode of right arm numbness in in September 2012 followed by right leg weakness in May of 2013 and MRI consistent with MS. He began on DMF as disease-modifying therapy in October 2013. His absolute lymphocyte count (ALC) dropped to 600 in July 2014 and reached a nadir of 400 in February 2014. Potential change in therapy was discussed however ALC stabilized at 500 in December 2015 and April 2016. He reported no infections during this time. In August of 2016 the patient developed rigors with fever to 102 Fahrenheit. He had intractable cough, myalgias, and malaise. Chest x-ray revealed bilateral patchy infiltrates concerning for

pneumonia. He received an intramuscular injection of ceftriaxone with little response after which he was started on an oral course of levofloxacin and began to improve. Urine antigen test for *Legionella* was positive. Investigation revealed no report of any outbreak of Legionnaires' disease at the patient's home, work or fitness center. He reported no atypical exposures. He fully recovered with completion of the course of levofloxacin.

**Conclusion:** We present this case of Legionnaires' disease in a patient with RRMS on DMF therapy to add to the body of literature on infections encountered in lymphopenic patients on this medication.

## Disclosure

Dr. Rachel Brandstadter: nothing to disclose

Dr. Ilana Katz Sand: nothing to disclose

## EP1657

### Brain atrophy and disease free status over 3 years in multiple sclerosis patients under interferon beta 1a subcutaneous treatment

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Percentage of brain volume change (PBVC) has been suggested as a potential marker of MS disease progression, however, no clear relationship between PBVC and disease free status was clearly described yet. The objective of the study was to evaluate the relationship of PBVC and disease free status in MS patients under interferon beta 1-a subcutaneous treatment (IFN-beta) during 3 years of follow up.

**Methods:** RRMS patients, with less than three years from disease onset, EDSS  $\leq 3$  and in which IFN beta 1-a 44 mcg was indicated were included. MR scans were acquired 3 to 6 months after the initiation of IFN beta 1-a treatment and every 12 months after during 3 years. Demographic, clinical and structural parameters from the MR scan, during the 3 years of follow up were analyzed and compared between patients with disease free status and no disease free status patients. Disease free status was defined as the absence of a) three month confirmed disability progression defined as an increase in EDSS score of 1.0; b) confirmed relapses; c) new/enlarged T2 lesions. PBVC from baseline to months 12, 12 to 24, 24 to 36 was compared between groups.

**Results:** 87 patients, mean age  $33 \pm 6$  years, 57 (65.5%) women were included. The mean EDSS of the population was  $2.1 \pm 0.5$ , follow up time  $40 \pm 4.3$  months. Disease free status was reached by 31 patients at year 3. PBVC from baseline to months 24 in disease free status patients was -1.1 % vs. -1.54 % in no disease free status patients ( $p < 0.001$ ) and from baseline to month 36 it was -1.43% vs. -2.1% ( $p < 0.001$ ) in disease free and no disease free status respectively.

**Conclusion:** At 3 years follow up, patients who received IFN beta 1a and were disease free had lower PBVC compared to patients with disease activity.

## Disclosure

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## EP1658

### Characterising properties of dimethylfumarate on innate and adaptive immunity: longitudinal data from MS patients

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**Introduction:** The mode of action of dimethylfumarate (DMF), an immunomodulatory treatment for relapsing-remitting multiple sclerosis (RRMS), has not yet been fully elucidated. While in-vitro experiments and animal studies suggest effects on immune cell survival, cytokine secretion and oxidative stress response, a proof from human ex-vivo studies is lacking.

**Methods:** Blood samples were collected from twenty well-characterized RRMS patients at baseline and after 3, 6 and 12 months of DMF treatment and an age- and gender-matched cohort of healthy individuals at 0 and 3 months. Peripheral blood mononuclear cells (PBMCs) were separated and cryopreserved for flow cytometry and immunoassays. Leukocyte subpopulations and cytokine secretion ex-vivo and upon in-vitro stimulation were recorded. T cells were assessed for their levels of reactive oxygen species (ROS) and their proliferative capacity. Response of monocyte activation markers as well as NFkB and MAPK pathways to DMF was analysed.

**Results:** Upon DMF treatment all lymphocyte subpopulations dropped significantly over the course of 12 months with cytotoxic and effector T cells being affected most drastically. In vitro DMF treatment lead to increased lymphocyte cell death which was potentiated by oxidative stress. In line with this result a significant increase of cytosolic ROS levels after 3 months treatment was detected. DMF inhibited proliferation of T cells in-vitro ( $CD8 > CD4$ ). Interestingly, this anti-proliferative effect decreased under treatment. While in-vitro stimulation with DMF resulted in an increased secretion of pro- and anti-inflammatory cytokines, no according longitudinal effects were observed. In-vitro DMF treatment reduced NFkB (p65) translocation to the nucleus. Consistent with this result the activation of antigen presenting cells (APCs) was decreased both in-vitro and ex-vivo.

**Conclusion:** This study translates knowledge from in-vitro and animal studies on DMF into the clinical setting. Our data suggest that DMF not only alters lymphocyte composition but also has profound effects on proliferation. In addition it also acts on innate immunity by reducing the activation status of APCs by reducing NFkB activation.

## Disclosure

This study was supported by an Investigator Initiated Trial grant from Biogen.

Tobias Derfuss received speaker fees, research support, travel support, and/or served on Advisory Boards or Steering Committees of Novartis Pharma, Merck Serono, Biogen, Teva, Bayer-Schering, GeNeuro, Mitsubishi Pharma, MedDay, Roche, and Genzyme.

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#### EP1659

##### **RAM-589.555 induces B-cell apoptosis during acute multiple sclerosis relapse: in-vitro study**

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**Background:** Acute multiple sclerosis (MS) relapses are a major factor that contributes to permanent neurological disability in MS patients. The current use of corticosteroids in the treatment of acute relapse has no effect on the sustained residual disability. Therefore, there is a need for a better treatment of acute MS relapses to reduce relapse residual disability. Recently, we have designed an innovative Polymerase I inhibiting compound, RAM-589.555, that suppresses ribosomal biogenesis and activates apoptosis as an innovative therapeutic approach to ameliorate MS relapse.

**Objective:** To evaluate effect of RAM-589.555 on B-cell apoptosis in-vitro during acute MS relapse as compared with methylprednisolone (MP).

**Design and methods:** CD19+ B-cells lymphocytes were obtained from relapsing-remitting (RRMS) patients during acute MS relapse. Cells were incubated for 72h with RAM-589.555 in concentration of 50 and 100 nM or with 400 mg/ml MP. Thereafter, cells were stained with Annexin V for early and Annexin/PI for late apoptosis level (MBL). Samples were analyzed by FACS Calibur (BD, Germany) and data were evaluated using FLOWJo software (USA).

**Results:** Five RRMS patients, age  $40.8 \pm 3.1$  years, disease duration  $9.1 \pm 1.6$  years and EDSS increase during relapse  $\geq 2.0$  were included in the study. Incubation of B-cells with 50 and 100 nM RAM-589.555 or 400 mg/ml MP increased early apoptosis by 2.6 ( $p=0.002$ ), 3.5 ( $p=0.001$ ) and 2.5 ( $p=0.01$ ) folds, respectively. Late apoptosis of B-cells were increased by 7.5 ( $p=4.69E-06$ ) and 8.9 ( $5.73E-06$ ) times using 50 and 100 nM RAM-589.555 respectively, and significantly less by MP ( $p=0.01$ ).

**Conclusion:** As compared to MP, RAM-589.555 significantly increased late apoptosis of B-cells obtained from RRMS patients in acute relapse. These findings suggest RAM-589.555 as a potential treatment for acute MS relapse.

#### **Disclosure**

Michael Gurevich: contracted research (Biogen Idec, Teva, Merck)

Anat Achiron: Consulting fees (EMD Serono, Genzyme, Roche); contracted research (Bayer, Biogen Idec, EMD Serono, Genzyme, Roche).

Anna Feldman: nothing to disclose

#### EP1660

##### **Is brain atrophy of multiple sclerosis patients treated with fingolimod different from those treated with interferon at high doses?**

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**Background:** SIENA is a free algorithm, part of the FSL toolkit ([www.fmrib.ox.ac.uk](http://www.fmrib.ox.ac.uk)) that allows the direct quantification of brain atrophy from serial MR images. It has been applied in numerous studies of MS, investigating brain atrophy in people who have experienced a CIS and patients with RRMS, SPMS and PPMS.

**Purpose:** To determine and to compare the Percentage of Brain Volume Change of two groups of MS patients treated on Interferon B1a sc or Fingolimod.

**Methods:** 63 patients (16 male and 47 female) with Relapsing Remitting MS and a Kurtzke Expanded Disability Scale Score (EDSS) of 0-5.0 were included in a prospective study of Fingolimod (36 patients) or Interferon B1a sc (27 patients) in RRMS. All patients were followed up for a minimum period of 1 year. Every three months disability was assessed by different neurological scale. Percentage of Brain Volume Change (PBVC) was measured by an automated segmentation of SIENA (ABACUS).

**Results:** Patients on Fingolimod 0.5 mg achieved a Percentage of Brain Volume Change of  $-0.48 \pm 0.6\%$ . Patients on Rebif achieved a Percentage of Brain Volume Change of  $-0.30 \pm 0.9\%$ . There was no statistical difference between these two groups.

**Conclusions:** Although the drugs are positioned at different levels of effectiveness, this measure of whole-brain atrophy provided similar data regarding these two immunomodulators. Further investigations are required.

#### **Disclosure**

JLRP nothing to disclose

#### EP1661

##### **Lymphocytes subsets after one year of dimethylfumarate treatment in multiple sclerosis: a real life study**

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**Objectives:** Dimethylfumarate (DMF) is used to treat relapsing multiple sclerosis and causes lymphopenia in a subpopulation of patients. Much remains to be understood about how the drug affects lymphocyte subsets. Our objective was to characterize changes in lymphocytic phenotype induced by DMF and if these changes are transient or persistent after 1 year of treatment.

**Materials and methods:** Peripheral blood samples were collected from 38 consecutive DMF-12 months-treated patients at our multiple sclerosis center at 3 different time points: before treatment start, after 6 months and 12 months of DMF treatment.



Leucocytes count, lymphocytes count and lymphocyte subsets (CD3+, CD4+, CD8+, C20+ and NK cells) were analyzed by flow cytometry, CD4/CD8 ratio was also evaluated.

**Results:** The total leucocytes count resulted unaffected by treatment. Lymphocyte count was significantly lower after 6 months of DMF treatment with persistent lower levels after 12 months (mean:  $1.83 \times 10^9/L$  pre-treatment, SD 0.46; 1.31 after 6 months, SD 0.51; 1.21 after 12 months, SD 0.40;  $p < 0.001$ ). All lymphocyte subsets, apart from NK cells, resulted significantly affected by treatment. CD3+ cells were significantly lower after 6 and 12 months of DMF (1448 cells/mm<sup>3</sup>, SD 569; 848, SD 311; and 810, SD 325;  $p=0.002$ ). CD4+ cells were significantly lower after 6 and 12 months of DMF as well (922 cells/mm<sup>3</sup>, SD 352; 606, SD 207; 567, SD 201;  $p=0.006$ ). CD8+ cells were the more affected subset, significantly lower at 6 and 12 months (481 cells/mm<sup>3</sup>, SD 239; 229, SD 130; 229, SD 140;  $p < 0.001$ ). C20+ cells were also mildly affected (290 cells/mm<sup>3</sup>, SD 181; 189, SD 107; 191, SD 83;  $p=0.044$ ). A significantly higher CD4/CD8 ratio at 6 and 12 months (2.16, SD 0.74; 3.3, SD 1.6; 3.3, SD 1.8;  $p < 0.001$ ) was detected.

**Discussion and conclusions:** The results of our real life study, though small, are consistent with those previously reported at 6 months and confirm the lowering of lymphocyte levels as an effect of DMF. CD8+ cells seem to be the more affected subset. Lymphocytes subsets changes are confirmed at 12 months, implicating a persistent alteration of the immune cellular profile under DMF treatment, which may be clinically relevant. Much remains to understand if these changes may be considered surrogate markers for efficacy and if safety implications have to be raised due to relative immunosuppression.

## Disclosure

Sara La Gioia: nothing to disclose  
Valeria Barcella: nothing to disclose  
Marta Zaffira Conti: nothing to disclose  
Barbara Frigeni: nothing to disclose  
Clara Zanchi: nothing to disclose  
Marianrosa Rottoli: nothing to disclose

## EP1662

### Real Life comparative evaluation of dimethyl fumarate efficacy and tolerability in relapsing remitting multiple sclerosis patients switching from other treatments

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**Introduction:** Dimethyl fumarate (DMF) is an oral medication effective as a first-line treatment of relapsing-remitting multiple sclerosis (RRMS). However efficacy and safety profile of DMF as a second-line treatment is controversial. In this study DMF administration was compared in naïve patients and in patients switching from another first line therapy.

**Methods:** MS patients with relapsing remitting MS consecutively treated for at least 8 months with dimethyl fumarate at the Multiple Sclerosis Regional Reference Center of the Careggi University Hospital, were included and followed for a median time of 15 months. For the analysis the patients were stratified in three groups:

- 1) treatment naïve;
- 2) switching from another treatment because of:
  - a) low efficacy;
  - b) adverse events.

The primary end-point of the study was DMF efficacy in terms of annualized relapse rate (ARR). Others end points were EDSS score change over 12 months, safety and tolerability.

**Results:** The patients included were  $n=81$ : 19 naïve (group 1) and 62 switching from other treatments (group 2). Out of these, 20 switched for efficacy failure (group 2a) and 42 because of adverse events (group 2b). Group 1 had a ARR in the year before therapy higher than Group 2a and Group 2b ( $p=0.027$  and  $p=0.03$ ), lower disease duration ( $p=0.003$  and  $p=0.01$ ) and EDSS ( $p=0.001$  and  $p=0.0001$ ). During treatment ARR was 0.06, 0.04 and 0.13 respectively in each group ( $p=0.78$ ;  $p=0.29$ ;  $p=0.44$ ); the median EDSS change after 12 months of treatment was 0.16, 0.06 and 0.10 respectively in each group ( $p=0.448$ ); the percentage of patients showing a progression of disability was very similar between group 1 and 2b (10.5% vs 9.5%), but tended to be lower in group 2a (5%, not significant).

Adverse events occurred in 36% of the patients. The most common were leucopenia, flushing or gastrointestinal disorders, mainly of mild entity and without difference among groups. The percentage of patients who interrupted the treatment because of adverse events was 9%.

**Discussion:** DMF seems effective in naïve as well as in patients switching from other treatments; the type and number of adverse events are consistent with previous data.

## Disclosure

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## EP1663

### Radiological and cognitive outcomes among patients randomized to interferon beta, glatiramer acetate or fingolimod in PREFERMS

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**Background:** PREFERMS was a 12-month, phase 4, open-label study comparing treatment retention on fingolimod and on injectable disease-modifying therapy (iDMT: interferon [IFN] beta or glatiramer acetate [GA]) in patients with relapsing multiple sclerosis. One treatment switch was allowed for any reason after  $\geq 3$  months, or before for efficacy or safety. At end of randomized treatment (EoRT), patients had received only randomized therapy. At end of study (EoS), randomized groups were a mix of patients exposed only to randomized treatment and those who had switched. In total, 58.1% of patients switched to fingolimod from IFN or GA and 6.2% switched to iDMT from fingolimod.

**Objective:** To compare patient outcomes on fingolimod and on different iDMT classes before (EoRT) and after (EoS) any treatment switches.

**Methods:** In PREFERMS (N=875), patients who were treatment-naïve or previously treated with iDMT were randomized 1:1 to fingolimod or to preselected IFN or GA. Exposure-adjusted percent brain volume loss (BVL) and percent cortical grey-matter volume loss (cGMVL) and change in oral Symbol Digit Modalities Test (SDMT) scores were analysed *post hoc* at EoRT and at EoS by treatment assignment at randomization (fingolimod, n=433; GA, n=231; IFN, n=197). Analyses were for hypothesis generation only.

**Results:** At EoRT, median BVL from baseline in the fingolimod and GA groups was 0.37% (n=370) and 0.46% (n=127), and at EoS was 0.40% (n=382) and 0.40% (n=194). Greatest BVL was in the IFN group at EoRT (0.85% [n=119]) but had reduced by EoS (0.59% [n=167]). At EoRT, median cGMVL from baseline in the fingolimod and GA groups was 0.02% (n=327) and 0.12% (n=53), and at EoS was 0.03% (n=348) and 0.12% (n=160). Greatest cGMVL was in the IFN group at EoRT (0.48% [n=56]) but had reduced by EoS (0.28% [n=137]). At EoRT, least-squares (LS) mean oral SDMT scores (95% confidence interval [CI]) had increased more in the fingolimod than in the GA group (3.5 [1.7, 5.2; n=73] vs 1.0 [-1.6, 3.6; n=35]) but were closer by EoS (3.2 [1.3, 5.1; n=73] vs 2.7 [0.0, 5.4; n=37]). At EoRT, LS mean score (95% CI) had decreased in the IFN group (-0.7 [-4.0, 2.6; n=30]) but had increased by EoS (2.5 [-1.0, 6.1; n=30]).

**Conclusions:** In PREFERMS, patients on fingolimod tended to have less BVL and cGMVL, and better cognitive scores than those on iDMT. At EoS, improved BVL and cGMVL in the IFN group, and cognition in the IFN and GA groups, might be due to the high proportion of switches to fingolimod.

## Disclosure

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**Xiangyi Meng, Lesley Schofield, Scott Kolodny and Nadia Tenenbaum** are employees of Novartis Pharmaceuticals Corporation.

## EP1664

### Profile of MS patients treated with alemtuzumab in real world

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**Introduction:** Alemtuzumab is a monoclonal antibody approved for the treatment of RRMS with clinical or radiological active disease. Alemtuzumab could be used as induction therapy or as second line treatment in the same way as in the clinical trials. But, it seems that the profile of patients treated with alemtuzumab in real world is quite different as in the clinical trials. The objective is to analyze the characteristics of patients who have started alemtuzumab in real life and the causes of switching.

**Methods:** Retrospective observational study including patients diagnosed with RRMS who received alemtuzumab in the last two years. Clinical examination and EDSS were performed before the treatment and every three months.

**Results:** We studied 20 RRMS patients of our MS center, 40% of them were men. The average age was 43 years old (32-57), and the time from the first symptom of MS was 14 years. The average EDSS before treatment was 5.5 (2.5-7.0). All had previously been treated modifying treatment of the disease: 25% with 2 treatments, 35% with 3 and 40% with 4 or more treatments. 95% had previously received Natalizumab and in 40% it was the previously treatment to Alemtuzumab (In 35% was Fingolimod and in 20% Tecfidera). 84.2% of patients have switched due to an increase of clinical and radiological activity; 32% only due to clinical activity and 10.5% radiological activity. 35.7% had 2 relapses in the previous year, and 28.6% had more than 3 relapses. 30% presented > 5 new hyperintense lesions in T2 and 50% had 2 or more contrast-detecting lesions.

**Conclusions:** The profile of MS patient starting Alemtuzumab in our center is very different from the clinical trials. In real life they are very active patients with a longer disease duration, higher EDSS and treated with two or more therapies before alemtuzumab. It was not used as induction therapy.

## Disclosure

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Marta Ortiz-Pica: Nothing to disclose

Ainhoa Arenaza-Peña: Nothing to disclose.

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## EP1665

### Switching from fingolimod to alemtuzumab in patients with active relapsing multiple sclerosis

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**Background:** Alemtuzumab has been shown to be efficacious in trials of early relapsing remitting multiple sclerosis (RRMS) in treatment naïve populations, and in those who have relapsed on injectable drugs. Despite limited clinical trial data, alemtuzumab is often used as a second or third-line agent in patients with longer disease durations and more established disability. A recent case series suggested a high risk of early relapses in patients switching from fingolimod to alemtuzumab.

**Objectives:** To investigate the frequency and predictors of relapse in RRMS patients switching from fingolimod to alemtuzumab.

**Methods:** We retrospectively analysed patients switching from fingolimod to alemtuzumab at the National Hospital for Neurology and Neurosurgery, London between 2015- 2017. Patient characteristics (age, sex, duration of RRMS, sequence of prior disease modifying therapies, relapses in the last 2 years, Extended Disability Status Scale (EDSS), and reason for switching treatments) and fingolimod treatment characteristics (duration of treatment, lymphocyte count, and wash out period) were collected.

**Results:** Fifteen patients were identified (mean age 38.5 (SD 8.75) years, 10 (66.7%) female, Mean EDSS 5.3 (SD 0.98), mean disease duration 10.2 (SD 6.34) years). The annualized relapse rate in the 2 years prior to switching to alemtuzumab was 1.07 (SD 0.59). The mean washout period between fingolimod and alemtuzumab treatment was 138 days. The mean follow-up on treatment with alemtuzumab was 9 months (range 0-18). 4/15 patients (26.7%) had relapses after a mean of 3.75 months after dosing (range 1-6). There was no difference in the annualized relapse rate, disease duration, lymphocyte count while on fingolimod or on starting alemtuzumab, or duration of the wash out period in patients with and without relapses after switching to alemtuzumab. Follow-up of the cohort is ongoing.

**Conclusion:** In this small case series of patients with active RRMS switching from fingolimod to alemtuzumab, one quarter had a relapse in the first year of treatment. Larger studies are required define risk factors for disease activity after switching from fingolimod to alemtuzumab.

## Disclosure

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WJ Brownlee: Nothing to disclose.

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## EP1666

### Teriflunamide and dimethyl fumarate: results from clinical practice

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**Introduction:** Teriflunamide (TRF) and dimethyl fumarate (DMF) are first-line oral immunomodulators approved for relapsing-remitting multiple sclerosis (MS) treatment. They have comparable efficacy with injectable drugs and are more convenient for patients.

**Aim:** To compare demographic and clinical characteristics between MS patients under TRF and DMF and to compare tolerability and efficacy.

**Results:** Clinical data from 30 MS patients under TRF and 50 MS patients under DMF was reviewed. All had relapsing-remitting type except for 2 patients under TRF who had secondary progressive type. MS patients under TRF were older ( $46.9 \pm 10.3$  vs  $36.5 \pm 9.4$ ,  $p < 0.001$ ) with no difference in gender ( $p = 0.49$ ). MS patients under TRF presented superior baseline EDSS (4 vs 1,  $p < 0.001$ ) but no difference in relapse rate for the last 12 months was found ( $0.5$  vs  $1$ ,  $p = 0.98$ ). The mean follow-up time was  $14.5 \pm 10.7$  months for DMF group and  $8.3 \pm 5.7$  months for TRF group. DMF and TRF were equally chosen for naïve patients. Treatment was changed to TRF or DMF due to adverse events in 55% and due to therapy failure in 26%. DMF had to be stopped in 7 patients (14%) due to intolerance (gastrointestinal symptoms, recurrent infections and lymphopenia) and in 3 patients (6%) due to clinical failure. TRF was stopped in 4 patients (13%) due to intolerance (toxic hepatitis, pancytopenia, epilepsy and recurrent infection) and in 1 patient (3%) due to severe alopecia and failure to prevent relapse. In those with more than 6 months of follow-up, the average relapse rate ( $p = 0.77$ ) and EDSS progression ( $p = 0.29$ ) were not different between groups.

**Conclusion:** TRF was the drug of choice for older and more disabled patients. Tolerability and efficacy were similar for both drugs.

## Disclosure

Nothing to declare.

## EP1667

### Multiple sclerosis outcome determination evaluating real differences after TimE (MODERATE): treatment variations and outcomes in Scotland

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**Introduction:** The long-term impact of Disease Modifying Treatments (DMTs) for people with Relapsing Remitting Multiple Sclerosis (pwRRMS) remains poorly characterised. Published data suggest considerable variation in DMT use, but suffer from numerous sources of bias. By identifying patients with similar disease severity in Scotland who are treated differently, MODERATE aims to compare outcomes in patients with and without DMTs, using Propensity Score Matching (PSM) to account for indication bias.



**Methods:** The Scottish Multiple Sclerosis Register was used to identify all pwRRMS diagnosed in 2010-2011 in 2 regional centres. PSM was used to identify DMT treated and untreated subjects with similar baseline characteristics. Nine covariates were used to calculate propensity scores for DMT initiation: age, gender, ethnicity, disease duration, initial relapse symptoms, number of relapses, first inter-attack interval and number of MRI lesions. Calliper distance was 0.2 for matching. Retrospective outcomes were collected, comparing pwRRMS who started a DMT within 1 year and remained on treatment versus pwRRMS never treated over 4 years.

**Results:** After exclusions for incomplete data, 245 patients were identified. 130(53%) had DMT started within one year of diagnosis, while 115(47%) did not. There was considerable overlap in propensity scores: 41% of untreated and 58% of treated pwRRMS were within the middle two quartiles for the whole cohort. PSM identified 62 matched pairs with similar disease severity at diagnosis, one of whom was treated and one of whom was untreated within 1 year of diagnosis.

Detection bias and missing data influenced outcome assessments, with treated patients being reviewed more frequently. Over 3 years, mean relapse number and severity in the treated and never treated group (39 pairs) showed no significant differences and 17.9%(treated) vs. 10.3%(untreated) pwRRMS had documented disability worsening. Over 5 years, 17.9% of the treated group and 5.1% of the never treated group were diagnosed with progressive disease ( $p=0.07$ ).

**Conclusions:** The initial decision to treat approximately half (124/245) of pwRRMS with DMTs in Scotland depends on factors unrelated to their disease or demographics. Propensity matched pairs have been generated for detailed outcome assessments evaluating the effects of DMT initiation and escalation. Initial retrospective analysis of the effect of early DMT initiation on disability has not demonstrated benefit over 5 years.

## Disclosure

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## EP1668

### Experience with tocilizumab in treatment of neuromyelitis optica

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**Objective:** To communicate our experience with the use of tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R), in a neuromyelitis optica (NMO) patient.

**Material and methods:** We present a 53-year-old patient diagnosed with seronegative neuromyelitis optica after an optic neuritis, a medulla oblongata lesion relapse and a longitudinally extensive transverse myelitis over 8 vertebral segments. The patient was initially treated with azathioprine but it had to be withdrawn due to severe pancytopenia. He was then treated with rituximab but developed a probable serum sickness reaction, so no consecutive dosing was administered. The patient had a medulla oblongata lesion relapse, requiring high dose methylprednisolone and plasma exchange for recovery. Treatment with tocilizumab was initiated as compassionate use at a dose of 8mg/Kg/month.

**Results:** The patient showed a good clinical response after 3 infusions. There were no new relapses or Magnetic Resonance Imaging inflammatory activity. He didn't develop cytopenia or any other associated complications.

**Conclusions:** Treatment with anti-IL-6 might be a safe and effective treatment option in NMO patients who don't respond or don't tolerate other traditionally used therapies.

## Disclosure

Virginia Meca-Lallana has received consulting or speaking fees from Almirall, Biogen, Genzyme, Merck Serono, Novartis, Roche, Terumo, Sanofi and Teva.

Virginia Meca-Lallana disclose neither conflict of interest in the elaboration of this abstract

## EP1669

### Safety and efficacy of dimethyl fumarate in a real-world relapsing-remitting multiple sclerosis population

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**Background:** Dimethyl fumarate (DMF) is an oral immunomodulator approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) and available in Portugal since April 2015, based on two phase III clinical trials demonstrating its efficacy.

**Objectives:** The aim of this study is to evaluate post-marketing DMF safety and effectiveness in a real-world clinical population.

**Methods:** Observational study of patients with RRMS treated with DMF in our centre with at least 6 months of follow-up. Demographic and clinical characteristics, including Annual Relapse Rates (ARR), Expanded Disability Status Score (EDSS), previous treatments, change in Magnetic Resonance Imaging (MRI) lesion load, adverse effects (AE), treatment duration and reason for discontinuation were examined.

**Results:** Eighty-four patients were included, 57 (67.9%) females. Mean age and mean disease duration were  $41.5 \pm 11.9$  years and  $8.9 \pm 7.2$  years, respectively. Mean baseline EDSS was  $1.7 \pm 1.7$ . Seventy (84.5%) patients received prior first-line disease modifying therapies (DMT), 2 (2.4%) patients received prior second-line DMT and 12 (14.3%) were treatment naïve. Mean follow-up was  $15.1 \pm 7.8$  months; 48 (57.1%) patients with at least 12 months of DMF treatment. Most frequent AE were flushing ( $n=45$ , 53.5%) and gastrointestinal symptoms ( $n=47$ , 55.9%). Lymphopenia was present in 22 (26.2%) patients (11 grade I, 6 grade II and 5 grade

III). Eleven (13.1%) patients experienced infections. Ten (11.9%) patients discontinued therapy due to AE (n=7), disease activity (n=2) and own initiative (n=1).

In total, 74 (88.1%) patients were relapse free at the end of follow-up. Mean interval between DMF start and first relapse was  $2.2 \pm 1.4$  months.

Considering the population with at least one year of follow-up (n=48), there was a 62.1% decrease in the ARR ( $0.58 \pm 0.94$  vs  $0.22 \pm 0.55$ ,  $p=0.002$ ), but no effect was observed regarding mean EDSS ( $1.92 \pm 1.76$  vs  $1.96 \pm 1.91$ ,  $p=0.667$ ). Among these patients, 27 (56.3%) performed a control MRI, 18 (66.7%) achieved No Evidence Disease Activity (NEDA), 9 (33.3%) had new MRI T2 lesions and 3 (11.2%) had new MRI T1-gadolinium-enhancing lesions.

**Conclusions:** Despite the incidence of some AEs (such as flushing and gastrointestinal side effects) was mildly increased than that reported in clinical trials, our observational data confirm the good tolerability and safety of DMF. This audit of DMF showed it significantly reduced relapse rates in this RRMS population.

## Disclosure

Ariana Barros: nothing to disclose;

João Sequeira: nothing to disclose;

Ary Sousa: nothing to disclose;

Carlos Capela: nothing to disclose;

Rui Pedrosa: nothing to disclose.

## EP1670

### Disease modifying therapy use in multiple sclerosis patients with comorbidities

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**Introduction:** Pivotal trials of multiple sclerosis (MS) disease modifying therapies (DMTs) typically exclude patients with significant comorbidities. This leads to uncertainty about the safety of DMTs in patients with comorbidities. Several studies have suggested that comorbidities negatively impact MS disease course, meaning patients with comorbidities may need to switch DMTs more frequently.

**Methods:** A database query for relapsing-remitting MS patients visiting the Mellen Center after 1 January 2010 was conducted. Chart review was completed to determine each patient's DMT history and whether or not they have hypertension (HTN), hyperlipidemia (HLD), diabetes (DM), or obstructive lung disease (OLD). A linear regression model was used to determine associations between comorbidities and the total number of DMTs used by a patient. Covariates used for adjustment included age, race, gender, disease duration, insurance type, median household income by zip code, depression, and smoking status. A parsimonious model using only significant predictors from the larger model was also constructed and tested for interactions.

**Results:** The analysis included 2,702 patients. The mean age was 47.9 years, mean disease duration was 11.2 years, and the mean number of DMTs was 2.1. In the larger model, male gender was significantly associated with a higher number of DMTs used ( $\beta = .131$ ,  $p=0.03$ ), while disease duration

( $\beta = -0.016$ ,  $p < 0.001$ ), HTN ( $\beta = -0.129$ ,  $p=0.02$ ), and HLD ( $\beta = -0.13$ ,  $p=0.03$ ) were significantly associated with fewer DMTs used. The results from the parsimonious model were similar and no statistical interaction was found with disease duration. When the model was applied to those with disease duration  $< 10$  years only, the relationship between disease duration and number of DMTs disappeared.

**Conclusions:** Patients with HTN and HLD used fewer DMTs, whereas DM and OLD had no association with the number of DMTs used. This may be because of concern about the safety of certain DMTs in patients with HTN and HLD. Interestingly, male gender was associated with more DMTs used. This may be due to a more aggressive disease among men requiring more treatment escalation. Alternatively, men may be less cautious and willing to try DMTs with more inherent risk. The inverse relationship between disease duration and number of DMTs used was unexpected. We theorize that this may be related to individuals diagnosed when fewer DMT options were available who never went on to change treatments.

## Disclosure

Devon Conway has received research support paid to his institution by Novartis Pharmaceuticals.

Sarah Planchon has nothing to disclose.

Daniel Ontaneda has received grant support from the NIH, NMSS, Novartis, Genzyme, and Genentech; and consulting fees from Genentech and Biogen Idec.

## EP1671

### Infusion-related reactions with ocrelizumab in phase III studies

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**Background:** Ocrelizumab (OCR) is an FDA-approved, humanised, CD20<sup>+</sup> B cell-selective monoclonal antibody for the treatment of relapsing (RMS) and primary progressive (PPMS) multiple sclerosis. Infusion-related reactions (IRRs) in OCR Phase III studies, including the separate double-blind, double-dummy OPERA I and II studies (RMS; OCR N=825; comparator: interferon  $\beta$ -1a 44  $\mu$ g three times weekly; NCT01247324 and NCT01412333) and ORATORIO (PPMS; comparator: placebo; NCT01194570) have been reported.

**Objective:** To define the pattern and characteristics of OCR IRRs in the prespecified pooled analysis of OPERA I and OPERA II, and ORATORIO.

**Methods:** OCR was given as 600 mg infusions every 24 weeks in OPERA I and OPERA II (96-week controlled period; 1<sup>st</sup> infusion:  $2 \times 300$  mg infusions split by 14 days) and ORATORIO (at least 120 weeks' controlled treatment until a set number of disease

progression events was seen; 2 × 300 mg infusions split by 14 days). Pretreatment per protocol was methylprednisolone (MP) 100 mg intravenous (or equivalent); antihistamines and analgesics/antipyretics were recommended. Populations of interest were those with an IRR ( $\geq 1$  or  $>1$ ), a Day 1 IRR (with/without  $\geq 1$  later IRRs) and those without Day 1 IRRs with a later IRR. Subgroups were also analysed by pretreatment.

**Results:** Overall, 283 of 825 (34.3%) of OCR recipients in the pooled OPERA analysis had  $\geq 1$  IRR; of these, 123 patients (14.9%) had  $>1$  IRR. 227 patients (27.5%) had an IRR on Day 1, of which 106 patients (12.8%) had a further IRR; 56 patients (6.8%) had an IRR after not having an IRR on Day 1. Most IRRs were mild to moderate in severity and generally manageable including by infusion adjustments; one life-threatening IRR (Day 1; bronchospasm; MP alone pretreatment) and no fatal IRRs occurred. 11 patients (1.3%) discontinued due to IRRs. Fewer IRRs were seen in patients pretreated with MP + antihistamines ( $N=120$ ;  $\geq 1$  IRR, 29.2% [ $n=35$ ];  $>1$  IRR, 9.2% [ $n=11$ ]; Day 1 IRR, 19.2% [ $n=23$ ]) vs other pretreatment groups ( $\geq 1$  IRR, 31.2–52.6%;  $>1$  IRR, 14.5–21.6%; Day 1 IRR, 24.9–49.5%). ORATORIO study results will be presented.

**Conclusions:** IRRs were a common adverse event experienced by 34.3% of patients ( $\geq 1$  IRR) and most frequently occurred at the first vs later infusions. IRRs were generally mild to moderate in severity, manageable (including infusion adjustments) and less frequent with a combination of premedication with MP + antihistamines before each infusion vs other pretreatment groups.

## Disclosure

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X. Montalban has received speaker honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion,

Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Teva and Trophos. C. Pozzilli has served on scientific advisory boards for Actelion, Biogen, Genzyme, F. Hoffmann-La Roche Ltd, Merck Serono, Novartis, Sanofi and Teva, and has received consulting and/or speaking fees, research support and travel grants from Allergan, Almirall, Biogen, Genzyme, F. Hoffmann-La Roche Ltd, Merck Serono, Novartis, Sanofi and Teva.

C. Chognot is an employee of F. Hoffmann-La Roche Ltd.

L. Julian is an employee and shareholder of Genentech, Inc.

H. Koendgen is an employee and shareholder of F. Hoffmann-La Roche Ltd

H. Zheng is an employee of Genentech, Inc.

J.S. Wolinsky has served on advisory boards, data monitoring or steering committees, has consulting agreements, or received speaker honoraria from the following entities: AbbVie, Academic CME, ACTRIMS, Alkermes, Bayer HealthCare, Biogen, Bionest, Celgene, Clene Nanomedicine, CMSC, ECTRIMS, Forward Pharma A/S, MedDay Pharmaceuticals, Novartis Pharmaceuticals, PRIME, Roche Genentech, Sanofi Genzyme, Strategic Consultants International, Takeda, Teva Pharmaceuticals and WebMD; royalties are received for outlicensed monoclonal antibodies through Uthealth from Millipore Corporation.

## EP1672

### Cyclophosphamide in the treatment of multiple sclerosis.

#### Can the “elders” protect against neurodegeneration?

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**Background:** Cyclophosphamide(Cy) is used as an induction therapy for aggressive relapsing-remitting multiple sclerosis(RRMS) and possibly for progressive types of the disease(primary or secondary progressive - PP or SP). The aim of this observational study was to identify determinants of disability improvement in patients receiving monthly(MO) infusions of Cy.

**Methods:** 91 MS patients (57 females and 34 males, mean age: 47.9, range: 26–75, mean duration of disease: 14.2 years, range: 0–46, median Expanded Disability Status Scale-EDSS: 6.0, range: 1.5–8.0), 7 (7.7%) with RRMS, 56 (61.5%) with SPMS, 22 (24.2%) with PPMS and 6 (6.6%) with relapsing progressive MS (RPMS) were included. The median number of MO Cy infusions was 3 (range: 1–21). The median MO Cy dose was 700mg/m<sup>2</sup>BSA (range: 500–1,500mg). Previous therapy (i.e. none, disease modifying drugs, immunosuppressive drugs or both) and the presence of 1 or more Gd<sup>+</sup> lesions before treatment was recorded. Disability improvement(DI) was defined as one point change in EDSS at the time of each patient's evaluation after the last infusion. Univariate tests (Student's t-test and chi-square test) and a Cox proportional hazard model was employed to ascertain determinants of improvement with Cy-therapy.

**Results:** 63 patients (69.2%) were identified with DI. The response rate across MS types was RRMS/RPMS: 69.2%, SPMS: 69.6% and PPMS: 68.2% ( $p=0.99$ ). Univariate test revealed that gender, age, duration of MS, EDSS at Cy onset, previous therapy



and Cy cumulative dose did not affect Cy response. The number of patients with DI was significantly higher in patients with no Gd+ lesions at Cy commencement than patients with at least one Gd+ lesion (77.5% vs. 40%,  $p=0.003$ ). Absence of Gd+ lesions was significantly related to disability improvement after Cy-therapy (HR: 2.56, 95%CI 1.16-5.66,  $p=0.02$ ), after controlling for age, gender, duration of disease, EDSS, previous therapy and disease type. Three patients on Cy-therapy developed urinary tract infection.

**Conclusions:** This study provides evidence for the significant DI of Cy-therapy even in MS patients with less neuroinflammatory types of the disease. Presumably, the ability of Cy to cross blood-brain barrier may account for the neuroprotective properties documented in this study. In an era of ongoing development of newer neuroprotective drugs, older and low cost treatments (i.e. Cy) may still confer significant DI in less neuroinflammatory or progressive types of MS.

### Disclosure

Dr. Maria Anagnostouli has received honoraria and research support from all pharmaceutical companies involved in MS therapeutics. Cyclophosphamide is solely available by a national health provider.

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Dr. Maria-Eleftheria has received honoraria and research support from all pharmaceutical companies involved in MS therapeutics. Cyclophosphamide is solely available by a national health provider. Dr. Elisavet Andreadou has received honoraria and research support from all pharmaceutical companies involved in MS therapeutics. Cyclophosphamide is solely available by a national health provider.

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Mr. Georgios Karagiorgis nothing to disclose

Mrs Panagiota Dimopoulou nothing to disclose

Mrs Paraskevi Katsika nothing to disclose

Mrs Pinelopi Koutsoudaki nothing to disclose

### EP1673

#### Severe acute non-immune thrombocytopenia during the first cycle of treatment with alemtuzumab

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**Objective and background:** Alemtuzumab (ALZ) is a monoclonal antibody approved for the treatment of Multiple Sclerosis (MS). Severe Immune Thrombocytopenia (ITP) has been reported as a side effect up to 1% within 14-36 months after the first dose

of ALZ. It has also been reported a decrease in the platelet count during the infusion, but always within normal limits. The objective of this paper is to report a case of severe acute non-immune thrombocytopenia during the first cycle of treatment with ALZ.

**Methods:** We present a case of severe acute non-immune thrombocytopenia, reversible and self-limiting, after the first dose on the first cycle of treatment with ALZ.

**Results:** 54-year-old woman with Relapsing-Remitting MS and 15 years evolution that despite receiving different treatments, has continued to present outbreaks; finally opting for ALZ treatment. After the first infusion, platelets 48000 UL were observed (201000 UL levels prior to treatment), no bruising and no evidence of bleeding. Treatment was suspended and platelets normalized, 155000 UL 72 hours later; so ALZ treatment was completed with good tolerance.

**Conclusions:** In the light of the approval of new MS treatments, it is important to pay attention to the potential onset of new side effects in our patients, as is our case, a severe non-immune thrombocytopenia during ALZ infusion.

### Disclosure

Authors: Nothing to disclose

## Neuroprotection and Repair

### EP1674

#### Contribution of K<sup>+</sup> channels and P2X7 receptor in 7-ketocholesterol - induced lipotoxicity on 158N murine oligodendrocytes: new pharmacological targets to prevent oligodendrocytes dysfunctions in multiple sclerosis

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**Aims:** Imbalance in the homeostasis of K<sup>+</sup> ions contributes to the pathogenesis of multiple sclerosis (MS). 7-ketocholesterol (7KC) often found at increased levels in patients with MS is able to trigger numerous oligodendrocyte dysfunctions. We therefore studied the impact of 7KC on 158N murine oligodendrocytes, and determined its effect on the P2X7 ATP-dependent receptor channel, and on the Kv3.1 potential dependent-channel, which are involved in K<sup>+</sup> homeostasis.

**Methods:** 158N murine oligodendrocytes were cultured with 7KC in the absence or in the presence of 4-aminopyridine (specific K<sup>+</sup> channel blocker), diazoxide (ATP sensitive K<sup>+</sup> channel activator), or glibenclamide (ATP sensitive K<sup>+</sup> channel blocker). The activation of P2X7 was measured by flow cytometry with YOPRO1. Kv3.1b expression was determined by flow cytometry and western-blotting with a mouse monoclonal antibody (Sigma-Aldrich; ref: SAB5200030 (anti-kv3.1b)). The intracellular concentration of K<sup>+</sup> ([K<sup>+</sup>]<sub>i</sub>) was determined by flame photometry and the ratiometric approach using the PBFI-AM fluorescence indicator. 7KC-induced cell death was

evaluated by the crystal violet test as well as by mitochondrial depolarization and enhancement of the cytoplasmic membrane permeability measured by flow cytometry after staining with DiOC<sub>6</sub>(3) and propidium iodide, respectively. Overproduction of reactive oxygen species (ROS) was quantified with dihydroethidium.

**Results:** Positive correlations were found between P2X7 activation, Kv3.1b expression and intracellular K<sup>+</sup> level, overproduction of ROS, loss of transmembrane mitochondrial potential and increased plasma membrane permeability in 158N cells. The correlations were determined with the Spearman correlation test:  $r$  was in the range of 0.8 and  $p \leq 0.005$ .

**Conclusion:** Our data support that the lipid environment affects P2X7 activity and Kv3.1b channel expression and/or functionality, and that the subsequent rupture of K<sup>+</sup> homeostasis as well as enhanced [K<sup>+</sup>]<sub>i</sub> is related with oligodendrocytes damages. It is suggested that the ability to modulate K<sup>+</sup> homeostasis with drugs capable to modulate ATP and voltage dependent K<sup>+</sup> channels could constitute new pharmacological targets to prevent oligodendrocytes dysfunctions in multiple sclerosis.

### Disclosure

Maryem BEZINE, Thomas NURY, Rym BEN-KHALIFA, Anne VEJUX, Jérôme de SEZE, Mohamed EL-AYEB, Thibault MOREAU and Gérard LIZARD have nothing to disclose.

### EP1675

#### The Australian Alfred Alectuzumab Experience

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Relapsing Remitting Multiple Sclerosis (RRMS) is an increasingly prevalent condition. Treatments to date have focused on stabilising the inflammatory aspect of disease and maintaining current level of function. Alectuzumab (Lemtrada®) an anti-CD52 monoclonal antibody is known to reduce disease activity and disability accumulation in primary drug trials. The Australian MS population is a unique demographic to study as there are no barriers to access or funding for any of the highly effective therapies at any stage of the MS disease process.

**Aim:** To assess the treatment effect of Alectuzumab for RRMS in an Australian centre, and ascertain if patient outcomes are improved with this new aggressive therapy.

**Hypothesis:** Patients with an EDSS (Expanded Disability Scoring Status) of 3-4.5 are likely to develop increasing disability from RRMS and will benefit most from new aggressive treatments.

**Methods:** 15 patients were treated for RRMS at Alfred Health with Alectuzumab and followed up between 2 and 15 months (average 8 months) with clinical review and EDSS assessment. There were 11 females and 4 males with an average MS disease duration of 7 years.

**Results:** The average EDSS score prior to commencement of Alectuzumab was 6.1. The average EDSS following treatment was 2.73 revealing that patients treated with Alectuzumab had an average EDSS reversal of 3.4. All the patients were treated with highly effective MS therapies prior to Alectuzumab treatment. Most patients changed to Alectuzumab due to long term safety concerns with their previous therapies and not because of ongoing MS disease activity.

Additional sub-group analysis determined that patients with a pre-treatment EDSS between 3 and 4.5 had the greatest EDSS reversal compared to those with a pre-treatment EDSS < 2.5 or > 6 where

there was no significant change in EDSS. All patients had EDSS stabilisation following treatment.

**Conclusion:** All patients in this study received highly effective MS treatment prior to Alectuzumab. This new therapy not only stabilised EDSS scores, but in several cases lead to EDSS reversal. Our single centre experience suggests patients with EDSS scores of 3-4.5 are most at risk of accumulating disability and the most likely to positively respond to this new aggressive therapy.

### Disclosure

Dr Skibina and Dr Nesbitt have both previously received sponsorship from Genzyme to attend educational meetings

There are no additional meaningful disclosures

### EP1676

#### Attenuation of 7-ketocholesterol and 7β-hydroxycholesterol - induced lipotoxicity by dimethylfumarate, monomethylfumarate and biotin on 158N murine oligodendrocytes

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**Aims:** Mitochondrial dysfunctions and oxidative stress are involved in multiple sclerosis (MS) associated with lipid peroxidation leading to increased levels of 7-ketocholesterol (7KC) and 7β-hydroxycholesterol (7β-OHC). These compounds induce oxidative stress, inflammation and cell death. Therefore, it is important to identify natural and synthetic compounds to counteract their side effects. So, the eventual protective effects of dimethylfumarate (DMF) and biotin (Vit B8), used for the treatment of MS, and of monomethylfumarate (MMF), the main metabolite of DMF, were evaluated on 7KC- and 7β-OHC-treated oligodendrocytes.

**Methods:** Murine oligodendrocytes 158N were exposed to 7KC or 7β-OHC (50 μM, 24 h) without or with DMF, MMF (25 μM) or biotin (10-100 nM). The activities of 7KC and/or 7β-OHC without or with DMF, MMF and biotin were evaluated by complementary methods: phase contrast microscopy, crystal violet test (quantification of adherent cells), MTT test (measurement of succinate dehydrogenase activity), flow cytometry (measurement of the mitochondrial potential (ΔΨ<sub>m</sub>), O<sub>2</sub>•<sup>-</sup> and H<sub>2</sub>O<sub>2</sub> production, with DiOC<sub>6</sub>(3), dihydroethidine and dihydrorhodamine 123, respectively; measurement of plasmic membrane integrity with propidium iodide (PI) and fluoresceine diacetate (FDA)). Apoptosis and autophagy were evaluated with Hoechst 33342 and acridine orange, respectively, and by Western blotting with specific antibodies against uncleaved and cleaved caspase-3 and PARP, and LC3-I/II.

**Results:** The cytotoxic effects of 7KC were attenuated by DMF and MMF: cell growth inhibition, loss of cell adhesion, decrease of ΔΨ<sub>m</sub>, O<sub>2</sub>•<sup>-</sup> and H<sub>2</sub>O<sub>2</sub> overproduction, PARP and caspase-3 cleavage, nuclear condensation and fragmentation, and activation of LC3-I into LC3-II. Biotin attenuates 7β-OHC-induced cell death: the number of non-adherent cells is decreased as well as the number of cells with damaged membranes and/or dead cells identified with PI and FDA; the number of cells with depolarized

mitochondria is reduced, and the decrease of mitochondrial succinate dehydrogenase activity is attenuated. The side effects of 7KC and 7 $\beta$ -OHC were significantly reduced (Mann Whitney test,  $P < 0.05$ ) with DMF, MMF and biotin.

**Conclusion:** Major side effects of MS, oxidative stress and mitochondrial dysfunctions leading to cell death of oligodendrocytes, are attenuated by DMF, MMF and Biotin. These data support that these molecules could be of interest to prevent oligodendrocyte dysfunctions in MS.

### Disclosure

Randa SGHAIER, Amira ZARROUK, Thomas NURY, Anne VEJUX, Ahmed Slaheddine MASMOUDI, Thibault MOREAU and Gérard LIZARD have nothing to disclose

### EP1677

**Modifying the migration velocity of oligodendrocyte progenitors by altering the expression of PDGFR $\alpha$  via CRISPR-Cas9**  
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Oligodendrocyte progenitor cells (OPCs) are capable of remyelinating injured axons caused by multiple sclerosis (MS). Demyelinated axons secrete PDGF-AA to direct chemotactic migration of PDGFR $\alpha$ -expressing OPCs. Still, this mechanism is not sufficient to achieve robust remyelination given that inflammation and demyelination activate fibrous astrocytes and microglia. Fibrous astrocytes and microglia generate a glial scar, which obstructs OPCs to contact with the axon thereby, blocking remyelination. Here, we demonstrate that by modifying the expression levels of PDGFR $\alpha$  in OPCs migration velocity can be altered. We transfected vectors based on CRISPR-Cas9 system targeting PDGFR $\alpha$  gene promoter to alter protein expression. CRISPR-Cas9 stimulates genome editing by creating a double strand break (DSB) in a precise locus, thereby inducing DNA repair by either non-homologous end joining (NHEJ) or homology directed repair (HDR). Transfection of two different constructs directed to PDGFR $\alpha$  promoter into mouse derived OPCs resulted in efficient expression of GFP reporter protein. We did not observe significant ultrastructural differences between transfected and non-transfected cells in transmission electron microscopy (TEM). By means of immunogold TEM, we observed GFP bound to the plasma membrane and to intermediate filaments as well as, inside the nucleus. We next sought to assess the effect of our approach on OPC migration efficiency by chemotaxis assays. Transfected cells exhibited a significant reduction in terms of migration velocity. This effect was more evident in OPCs transfected with PDGFR $\alpha$ 1 promoter-Cas9, suggesting that regulation of PDGFR $\alpha$ -mediated signalling via CRISPR-Cas9 is a promising tool for the treatment of demyelinating lesions. Our current efforts are focused on transfecting a linear DNA sequence containing a strong promoter flanked by homologous arms together with the PDGFR $\alpha$  promoter-Cas9 plasmids. We expect that these genomic editions might increase OPC chemotactic migration efficiency and eventually, modified cells could be engrafted into lysocleithin injected mice to assess remyelination efficiency.

### Disclosure

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Jose Manuel Garcia Verdugo: Nothing to disclose  
Vicente Herranz Perez: Nothing to disclose  
Maria Jose Ulloa Navas: Nothing to disclose  
Maria del Carmen Gonzalez Calixto: Nothing to disclose

### EP1678

**Effect of erythropoietin on disease activity and conversion into multiple sclerosis after optic neuritis**

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**Introduction:** In the EAE model of optic neuritis, erythropoietin was particularly effective when given in combination with methylprednisolone, and proved to exert neuroprotective effects in humans, too. Yet it is unknown if erythropoietin has any effects on MRI activity in MS patients

**Methods:** We analyzed changes in cerebral lesion load by magnetic resonance imaging (MRI) in 35 patients from a double-blind, placebo-controlled, phase II study on erythropoietin in clinically isolated optic neuritis (ClinicalTrials.gov, NCT00355095). In the trial patients with acute optic neuritis were assigned to receive either 33,000IU recombinant human erythropoietin i.v. daily for three days, or placebo, as an add-on to methylprednisolone. MRIs were recorded at baseline and at weeks 4, 8, and 16.

**Results:** During the observation period there was no significant difference between the groups with respect to the change in absolute numbers of periventricular, juxtacortical, and infratentorial lesions including gadolinium-enhancing lesions. In ten of thirty-five patients we found MRI disease progression already within the observation period of 16 weeks. In 5 (14%) patients, we found a conversion into multiple sclerosis (MS) based on MRI progression only. These patients all received placebo. Another 5 patients showed MRI progression together with relapses. Three of these patients had received erythropoietin, two placebo.

**Conclusions:** After isolated optic neuritis erythropoietin treatment did not change MRI progression. However during follow-up early conversion to CDMS seemed to occur more frequently in the placebo-treated group.

### Disclosure

KW.S: no conflict of interest  
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P.P.: no conflict of interest  
K.S.: no conflict of interest  
R.P.: no conflict of interest

### EP1679

**Mapping proteomics changes induced by fingolimod in different regions of the brain and retina**

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**Purpose:** Fingolimod (FTY720) is widely used in the management of multiple sclerosis and is known to upregulate Akt and Erk neuroprotective survival signalling pathways in the neurons and astrocytes. The drug protects neurons against ischemic stroke and has also been shown to protect the retina against damage caused by experimental glaucoma. In this study, we aimed to investigate the molecular changes caused by fingolimod in the retina and different regions of the brain under normal conditions.

**Methods:** CBA/CaHarc mice were treated with the FTY720 drug (7.5 mg/kg i.p weekly) or vehicle control for 2 months. Retina and brain tissues (frontal cortex, hippocampus, cerebellum) were harvested and examined from drug treated and control mice (n=10). A multiplexed proteomics using chemical isobaric tandem mass tags (TMTs) using LC/MS was carried out. Detailed functional and protein-protein interaction analyses were performed using Ingenuity pathway analysis, STRING and Panther computational tools.

**Results:** FTY720 administration lead to differential proteomics changes in various regions of the central nervous system (CNS) particularly in the frontal cortex and cerebellum. Mass spectrometry revealed 29, 10, 1272 and 667 upregulated and 16, 22, 1361, 1265 downregulated proteins in the retina, hippocampus, frontal cortex and cerebellum respectively out of a total of >6000 proteins identified in each case. Computational analysis demonstrated several of the proteins associated with neuroprotective signalling were upregulated (e.g; Sphingosine 1 phosphate receptor 1 (S1PR1)  $p < 0.0001$ ; phosphatidylinositol 3-Kinase  $< 0.02$ ; insulin receptor  $< 0.001$ ; serpin a3k  $< 0.00001$ ) while markers associated with pro-inflammatory and apoptotic pathways (Caspase 1  $< 0.007$ ; caspase 3  $< 0.01$ ; Tumour necrosis factor (TNF) alpha  $< 0.0001$ ; tissue plasminogen activator (tPA)  $< 0.02$ ; interleukin 1R  $< 0.001$ ; interleukin enhancer binding factor 2 (ILF2)  $< 0.03$ ) were downregulated.

**Conclusions:** This study for the first time provides a comprehensive profile of proteomics changes in different CNS regions under normal conditions upon chronic fingolimod treatment. Protein quantification and computational analysis highlight that fingolimod not only promotes suppression of pro-inflammatory pathways, but also up-regulates neuroprotective pathways.

## Disclosure

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Mehdi Mirzaei: Nothing to disclose.

Alexander Klistorner: Nothing to disclose.

Stuart Graham: Nothing to disclose.

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## Long-term treatment monitoring

### EP1680

**Observational study to evaluate real-world effectiveness in multiple sclerosis patients treated with alemtuzumab in Germany: TREAT-MS study preliminary results**

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<sup>1</sup>Center of Clinical Neuroscience, Carl Gustav Carus University Hospital, Dresden, <sup>2</sup>Clinical Study Unit, Sanofi Deutschland GmbH, Frankfurt am Main, <sup>3</sup>Medical Affairs, Sanofi Deutschland GmbH, Neu-Isenburg, Germany

**Background:** Alemtuzumab, a humanised anti-CD52 monoclonal antibody, is approved in >60 countries for patients with RRMS. In 2 phase 3 studies, alemtuzumab administered in 2 annual courses 12 months apart had improved efficacy versus SC IFNB-1a over 2 years. In an extension, efficacy was durable over 6 years in the absence of continuous treatment, with manageable safety; long-term evaluation is ongoing (TOPAZ; NCT02255656). Real-world data on alemtuzumab use in clinical practice are limited.

**Goal:** Report preliminary real-world safety and effectiveness results from the ongoing TREAT-MS study (non-interventional long-Term study foR obsErvAtion of Treatment with alemtuzumab in active relapsing-remitting MS) of alemtuzumab in RRMS patients in Germany.

**Methods:** TREAT-MS is a 5-year, observational, longitudinal study of patients (max: 3200) treated with alemtuzumab according to German prescribing information, with prospective and retrospective data collection. Follow-up will continue for 48 months post last dose. Assessments: change from baseline (BL) in EDSS score; Physicians' Clinical Global Impression (PCGI) score; adverse events (AEs).

**Results:** As of April 27, 2017, 566 patients were screened; 547 (96.6%) were treated (537 received Course 1). BL characteristics: 71.0% female; mean (SD) age 35.5 (9.0) years (range, 16-62 years); time since first MS symptoms 7.7 (6.6) years; time since MS diagnosis 7.1 (6.3) years; relapses in 12/24 months before inclusion 1.7 (1.2)/2.3 (1.9). Immediate prior medication: fingolimod (23.4%); natalizumab (20.8%); interferon beta preparations (10.5%); glatiramer acetate (5.5%); others (15.8%); none (15.8%); unknown (7.8%). After alemtuzumab, mean (SD) and median EDSS estimates were stable from BL (3.0 [1.8], 2.5) to Month 12 (2.8 [1.8], 2.5) and Month 24 (2.7 [1.7], 2.5); mean PCGI score improved from 3.9 (1.3) at BL to 3.6 (1.2) at Month 12 and 3.4 (1.2) at Month 24 ( $P < 0.001$ ). Median PCGI was constant (4.0). Percentage rated slightly, borderline, or not ill: 33.9% (BL); 43.7% (Month 12); and 48.5% (Month 24). Safety profile was similar to previous clinical trials.

**Conclusion:** Patients in TREAT-MS have different BL characteristics compared with those in the registration studies (due to different prior medications), and showed stable EDSS and stable/improved PCGI scores through 2 years. TREAT-MS data will help provide additional guidance for optimising sequencing to/from alemtuzumab and monitoring of alemtuzumab-treated RRMS patients.

**Study support:** Sanofi.

## Disclosure

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### EP1681

**A retrospective claims analysis: compliance and discontinuation rates among anadians MS patients treated with disease-modifying therapies at 6, 12 and 24-months - Canadian real world experience**

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**Background:** Compliance to therapy has been associated with a reduced risk of relapse, reduced healthcare resource utilization and improved health-related quality-of-life in patients with multiple sclerosis (MS).

**Objective:** To assess compliance and discontinuation rates with Disease-Modifying Therapies (DMTs) in Canadian patients with Relapsing-Remitting MS (RRMS).

**Methods:** In this Canadian retrospective claims analysis based on Rx Dynamics® data from IMS Health Canada Inc., patients had ≥1 prescription filled for each DMT (oral: fingolimod, dimethyl fumarate (DMF), teriflunomide; injectable (BRACE): interferon beta-1a, interferon beta-1b, glatiramer acetate; infusible: natalizumab). Patients were considered compliant if the medication possession ratio (MPR) was ≥80%. Discontinuation rates were calculated based on patients who stopped therapy (60 day window) or who were switched to another DMT. Compliance and discontinuation rates were collected 6, 12 and 24-month periods (cohorts from 2013-2017, rolling 36 months total).

**Results:** Compliance and discontinuation data was collected after 6 month (n=12543, n=9460 respectively), 12 month (n=7665, n=7234) and 24 month (n=6047, n=6030) periods. The percentage of patients deemed compliant after 6, 12- and 24-months across Canada was higher for fingolimod (75%, 76%, 71% respectively), compared to natalizumab (72%, 73%, 56%), DMF (71%, 68%, 55%), and BRACE (52%, 46%, 35%) and comparable to teriflunomide (76%, 77%, 68%). Patients on fingolimod had the lowest discontinuation rate after 6, 12 and 24-month periods (26%, 25%, 29% respectively) compared to: BRACE (48%, 35%, and 55%); natalizumab (34%, 29%, and 49%) and DMF (31%, 30% and 43%); and similar to teriflunomide (26%, 25%, 31%).

**Conclusions:** The percentage of patients deemed compliant and treated with fingolimod was higher than for other DMTs but was similar to teriflunomide. Unlike other DMTs, the discontinuation rate with fingolimod did not significantly increase and the compliance rate with fingolimod remained stable over the 24-month period. The discontinuation rate of fingolimod was lower compared to other DMTs at all time points and was similar to teriflunomide. This analysis provides insight into short and medium term compliance and discontinuation of DMTs in a Canadian real-world setting. These findings may inform MS management strategies which may lead to improved clinical and economic outcomes.

## Disclosure

**Pierre Duquette:** has received honoraria for advisory boards, for CMEs from Novartis, Biogen-Idec, Genzyme, EMD Serono and Teva Neuroscience. He has taken part in Investigator-initiated trials funded by Novartis, Biogen-Idec, Genzyme and EMD Serono and has received funding from peer-reviewed agencies such as the Canadian Institutes for Health Research (CIHR) and the MS Society of Canada.

**Michael Yeung:** has received honoraria for consultation fees from EMD-Serono, Genzyme and Novartis, and the Canadian Agency for Drugs and Technologies in Health (CADTH/Health Canada), and research support from Biogen-Idec, Genzyme, Hoffmann-La Roche, Novartis, and Teva Canada Innovation.

**Robyn Schechter:** is an employee of Novartis Pharmaceuticals Canada Inc.

**Paola Haddad:** is an employee of Novartis Pharmaceuticals Canada Inc.

**Katherine Jobin Gervais:** is an employee of Novartis Pharmaceuticals Canada Inc.

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## EP1682

### A Swedish nationwide pharmaco-epidemiological study of the long-term safety and effectiveness of dimethyl fumarate (IMSE 5)

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**Background:** Dimethyl fumarate (DMF) is an oral therapy for relapsing-remitting multiple sclerosis (RRMS), the efficacy of which has been shown in phase II and III studies. However, post-marketing surveillance is important to determine the long-term safety and effectiveness in a real-world setting. DMF has therefore been included into the Swedish post-market surveillance study "Immunomodulation and Multiple Sclerosis Epidemiology" (IMSE).

**Objectives:** To follow-up the long-term safety and effectiveness of DMF in a real-world setting.

**Methods:** MS patients in Sweden are registered into the nationwide web-based Swedish Neuro registry (Neuroreg). The IMSE study includes descriptive data of adverse events (AEs), extended disability status scale (EDSS), MS severity scale (MSSS), symbol digit modalities test (SDMT), MS impact scale (MSIS-29), European quality five dimensions (EQ-5D) and Visual Analog scale (VAS) obtained from Neuroreg. Blood samples are collected at baseline and after 12 and 24 months of treatment. Drug survival was measured using the Kaplan-Meier curve and effectiveness measures were assessed using the Wilcoxon Signed Rank Test.

**Results:** 1820 DMF-treated patients have been included in the IMSE 5 study between March 25<sup>th</sup>, 2014 and April 30<sup>th</sup>, 2017 most of which have switched from interferons or glatiramer acetate (44%), 23% of the patients were treatment naïve (11% missing data on prior treatment). 91% of the patients have RRMS (4% missing data on MS phenotype). The mean treatment duration is 18.0 ± 11.1 months, the mean age at treatment start is 40.8 ± 11.0 years and 73% are female.

The one year drug survival was 74% and discontinuation was significantly more common among female than male patients ( $p < 0.05$ ).

In patients treated with DMF continuously for ≥24 months (n=669), significant improvements in mean values at 24 months of treatment compared to mean baseline values have been noted for MSSS by 24% ( $2.6 \pm 2.4$  to  $2.1 \pm 2.2$ , n=120); SDMT by 2%

(52.0 ± 10.8 to 53.0 ± 11.4, n=242); and MSIS-29 Psychological subscale by 15% (27.9 ± 23.0 to 24.3 ± 21.1, n=240). EDSS, MSIS-29 Physical subscale, EQ-5D and VAS did not improve significantly.

**Conclusions:** Neuroreg proves to function well as a post-marketing drug surveillance platform, providing data regarding drug effectiveness and AEs. DMF is generally well tolerated; however a longer follow-up period is needed to assess the real-world effectiveness and safety of DMF.

## Disclosure

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Åsa Leandersson has nothing to disclose.

Anders Berglund is employed at Biogen, Sweden

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Claes Martin has received honoraria for lectures and advisory boards from Merck Serono and Sanofi Genzyme.

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Tomas Olsson has received unrestricted research grants or honoraria for lectures or advisory boards from Biogen, Novartis, Merck Serono, Teva and Sanofi Genzyme.

## EP1683

### Clinical and economic evaluation of alemtuzumab compared to ocrelizumab in the treatment of relapsing forms of multiple sclerosis in the United States: a payer perspective

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**Background:** Alemtuzumab (ALEM) and ocrelizumab (OCR) each demonstrated improved clinical efficacy outcomes vs SC IFNB-1a in patients with active relapsing MS (RMS) in randomised phase 3 clinical trials over 2 years (y) (ALEM: CARE-MS I [NCT00530348]/CARE-MS II [NCT00548405]; OCR: OPERA I [NCT01247324]/OPERA II [NCT01412333]). ALEM demonstrated durable efficacy over 6 y in an extension (NCT00930553) in the absence of continuous treatment. OCR launched in the US at lower annual cost than other therapies.

**Goal:** To evaluate the relative clinical and economic benefit of ALEM vs OCR in patients with RMS in the US.

**Methods:** A Markov model (using British Columbia MS data to project disease progression) of patients transitioning in annual cycles through EDSS health states, was run from a US payer perspective. The modelled population represented demographic and clinical characteristics of pooled treatment-naïve and -experienced patients from CARE-MS I and II. ALEM and OCR efficacy inputs were derived from network meta-analysis. Compared to no treatment, the relative risk (95% CI) for reducing relapses was 0.31 (0.26-0.36) for ALEM and 0.35 (0.26-0.47) for OCR. The hazard ratio for slowing 6-month (mo) confirmed disability worsening was 0.41 (0.27-0.63) for ALEM and 0.46 (0.29-0.72) for OCR. For ALEM (12 mg/d IV; baseline: 5 d; 12 mo later: 3 d; as-needed retreatment: ≥12 mo after previous course for relapse/MRI activity), acquisition cost was \$103,749 in Y1 (Course 1) and \$62,250 in Y2 (Course 2) and all subsequent courses. For OCR, acquisition cost was \$65,000 annually. Administration and monitoring costs per year were lower for OCR than ALEM. Safety information was extracted from FDA-approved prescribing information.

**Results:** Over a 20-y horizon, 8.89 quality-adjusted life y (QALYs) and \$426,169 total costs were accumulated with ALEM vs 8.46 QALYs and \$908,742 total costs with OCR. Patients on ALEM had fewer relapses (mean: 7.1) compared with those on OCR (mean: 8.5). QALY loss due to adverse events was -0.126 for ALEM vs -0.006 for OCR. The OCR withdrawal rate and the assumption of ALEM durable efficacy over 6 y were identified as the most influential model parameters.

**Conclusion:** In this analysis, ALEM is projected to be cost-saving and more effective vs OCR. Results should be interpreted with caution as a head-to-head comparison is unavailable, but they offer evidence of economic and clinical benefits of ALEM vs OCR from a US payer perspective.

**Study support:** Sanofi.

## Disclosure

VC, NJ, DP, NC: Employees of Pharmerit International.

AS, CG, LH: Employees of Sanofi.

IM: Previously employed by Sanofi.



**EP1684****Regression of erythroblastemia in natalizumab-treated patients with multiple sclerosis after drug suspension**

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**Objectives:** Erythroblastemia has been previously reported as a frequent finding of natalizumab treatment in multiple sclerosis patients. Its long-term clinical or pathological implications are still to be understood. We investigated the persistence of erythroblastemia after natalizumab suspension.

**Materials and methods:** We retrospectively evaluated the blood samples of 15 subjects with erythroblastemia during natalizumab and who were withdrawn from treatment.

**Results:** All our patients had been treated with more than 12 natalizumab infusions and they suspended the treatment due to evidence of antiJCv antibodies. Erythroblastemia was present in all cases at the last blood sample before the last drug administration. Erythroblasts were absent in all blood samples of our patients after a mean time of 2.8 months (range 1-4 months) after drug suspension.

**Discussion and conclusions:** The prevalence of erythroblastemia has been previously reported to be significantly higher in patients treated with natalizumab compared to patients on other multiple sclerosis treatments. These previous data raised some issues on long term pathological implications. Our last findings support the hypothesis of erythroblastemia as a transient phenomenon during natalizumab treatment: it appears then acceptable to refrain from further diagnostic procedures during treatment in the absence of any other laboratory results suggesting underlying disorders. A larger sample of patients is needed to confirm our data.

**Disclosure**

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Barcella Valeria: nothing to disclose

Conti Marta Zaffira: nothing to disclose

Frigeni Barbara: nothing to disclose

Vedovello Marcella: nothing to disclose

Zanchi Clara: nothing to disclose

Rottoli Mariarosa: nothing to disclose

**EP1685****Case series: a specialty center 10 year experience with use of azathioprine in neuromyelitis optica spectrum disorders (NMOSD)**

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**Introduction:** The therapy of neuromyelitis optica spectrum disorders (NMOSD) targets early treatment and prevention of relapses as well as improvement of relapse-associated symptoms. Without adequate relapse prevention most patients will present a devastating stepwise accumulation of disability. Azathioprine was historically used for the management of multiple sclerosis and it is

currently widely used in the treatment of NMOSD. An increase in risk of cancer has been reported in patients with long term use of azathioprine for intestinal and rheumatologic diseases. There is no such description for patients with NMOSD. We report our experience with the long term use of azathioprine in NMOSD patients.

**Methods:** We conducted a retrospective medical record review of all Hospital das Clínicas da Universidade de São Paulo - Brazil patients who filled NMOSD 2015 criteria and were treated with azathioprine for at least 10 years.

**Results:** Of 375 reviewed records, 18 patients met inclusion criteria (4.8%); 17 were female and 1 was male, 17 were NMO-IgG seropositive. Median age was 44 years (27-56). Median time of disease was 15 years (10-39). Mean duration of treatment was 12.43 (SD = 3.16). Mean relapse/year rate prior and post introduction of azathioprine was 0.928 (SD = 0.478) and 0.131 (SD = 0.115) with a statistically significant reduction ( $p < 0.001$ ) on analysis. Eleven of the patients (61.1%) had been free of relapses for at least 5 years. Three patients (16.6%) had records of adverse events during the follow up: chronic B12 deficiency, pulmonary tuberculosis and breast cancer. At the time of the review 13 of the 18 patients (72%) were still receiving azathioprine, 1 had been switched methotrexate due to long exposure to azathioprine, 1 to rituximab due to failure of therapy and the remainder 3 had immunosuppression discontinued due to stability of disease.

**Discussion:** Adverse events are a concern for patients undergoing long term use of azathioprine; therefore screening is warranted. In our sample, azathioprine was considered relatively safe with only one report of malignancy (5.5 %) and effective in relapse prevention ( $p < 0.001$ ) at a 10 year follow up.

**Conclusion:** We believe the risks of adverse events are surpassed by the clinical benefits of azathioprine use, therefore we suggest a vigilant maintenance of therapy for responding patients with long use of the drug.

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**EP1686****Real World Evidence (RWE) on long-term persistence to medications for relapsing-remitting multiple sclerosis (RRMS) in the Australian community (REALITY)**

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 Griffith University, Gold Coast, QLD, Australia

**Background:** This study aimed to examine and compare patient persistence to all publicly-funded disease modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) in Australia.

**Method:** The Australian Government Medicare Database was used in this study. For patients to be eligible for the study they needed to have received a script for a reimbursed MS disease modifying therapy between September 2011 and February 2016. Patient demographics were summarized using mean and standard deviation or frequency percentage. Persistence was defined as a patient that remained on a DMT with a gap in scripts of no longer than 4 months. Individual patients could be included multiple times if they initiated a new DMT during the study period. Persistence was derived using the Kaplan-Meier method and hazard ratios (HR) calculated to compare persistence rates between different treatments; p-values were based on the log-rank test.

**Results:** A total of 720 unique patients were eligible for the study. The majority were female (73.5%) and aged between 36-65 (64%). These patients contributed 1827 observations that were used for analysis (i.e. 2.5 new initiations/patient). Overall the median persistence to therapy was 29.6 months with 67.7% of patients remaining on therapy for 12 months. The only DMT that had significantly better persistence compared to the overall average, was fingolimod (HR 0.65 (95%CI: 0.57-0.73; p< 0.001)). Patients had a median persistence of 60 months on fingolimod and 79.5% of patients were persistent at 12 months. Patients were significantly less persistent to interferon Beta-1a, interferon Beta-1b, glatiramer acetate and dimethyl fumarate (hazard ratios above 1.27 (p values all ≤ 0.001) whilst the remaining DMTs, teriflunomide and natalizumab, showed no significant difference from the average persistence.

**Conclusion:** In Australia, reimbursed MS patients were most persistent to fingolimod treatment amongst all DMTs. The implications of this superior persistence and how it may translate to differences in clinical effectiveness will be the subject of future studies.

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## EP1687

### Long-term real-life retrospective analysis on interferon β1-a use in RRMS patients in Finland

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**Objective:** To study the long-term real-life use of interferon β1-a sc tiw in relapsing remitting multiple sclerosis (RRMS) patients, and to investigate the duration of the treatment periods, the causes of treatment cessation, and changes in expanded disability status scale (EDSS).

**Methods:** Clinical data was drawn in two population based cohorts diagnosed for RRMS during 1990 to 2010 and 2010 to 2014. Patients treated with interferon β1-a sc tiw at the Tampere District University Hospital in Finland were included in the study. Baseline characteristics and study endpoints were summarized using descriptive statistics.

**Results:** Of the 680 patients diagnosed during 1990-2010, a total of 293 initiated with interferon β1-a sc tiw. The average first treatment period lasted 2.9 years (standard deviation SD 2.89). The EDSS at treatment start was 1.7 (mean, SD 1.56) and 3.4 at the follow up of 6.8 years (mean, SD 4.1). Of the 209 patients diagnosed during 2010-2014, a total of 68 initiated with interferon β1-a sc tiw. The average first treatment period lasted 2.1 years (SD 1.55). The EDSS at treatment start was 0.9 (mean, SD 1.08) and 1.3 at the follow up of 2.2 years (mean, SD 1.3). Of the 361 patients in both cohorts, 39.1 % of the patients did not switch treatment. A total of 36.1% switched treatment once. The activation of the disease was the most common cause for cessation of the treatment (24.1%). Other factors were low MXA titer (12.2%) and side effects (11.9%). A total of 53.7% did not have any treatment interruptions, 32.4% had one interruption.

**Conclusions:** Long-term compliance to treatment was observed in patients treated with interferon β1-a sc tiw.

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## EP1688

### The burden of treatment monitoring in disease modifying therapies in Europe and the United States

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**Background:** Increasingly, high efficacy infusion and oral disease modifying therapies (DMTs) possess extensive monitoring requirements during both treatment initiation and throughout the course of therapy.

**Objective:** To assess perceptions of the burden of monitoring requirements for multiple sclerosis (MS) treatments among healthcare professionals (HCPs) in both the 5EU (UK/Germany/France/Italy/Spain) and the United States.

**Methods:** The Ipsos Healthcare Global MS Therapy Monitor, a multi-centre cross-sectional survey of HCPs (mainly Neurologists;

MS nurses included in UK) is run on a bi-annual basis in 5EU and US since 1997 to collect de-identified perceptions and barriers to use of DMTs. HCPs are recruited from a large panel to be geographically representative within respective countries. HCP perceptions from Q4 (September through December) in 2013, 2014, 2015, and 2016 were analysed.

**Results:** 270 HCPs in 5EU (2013: N=265, 2014: N=275; 2015: N=269, 2016: N=275) and 100 HCPs in the US (2013: N=100, 2014: N=100; 2015: N=111, 2016: N=99) were included. 58.4% and 60.3% of HCPs in the 5EU and US, respectively, associated high efficacy DMTs (natalizumab, alemtuzumab, fingolimod, daclizumab) with initial and on-going monitoring. The strength of this perception decreased over time (68.9% and 80.5%, respectively in 2014 to 58.4% and 60.3% in 2016). Platform orals (teriflunomide, BG-12) were also frequently perceived to have monitoring requirements (46.9% and 55.6%, respectively). 11.5% (5EU) and 17.2% (US) of HCPs also perceived the monitoring of platform orals to be a barrier to prescribing; 19.8% (5EU) and 33.1% (US) perceived the monitoring of high efficacy DMTs to be a barrier. In comparison, very few HCPs in both regions considered monitoring as a barrier to use of the platform injectables (Interferon beta-1a and 1b, Glatiramer Acetate); 2.3% (5EU) and 1.4% (US).

**Conclusions:** HCPs in both the 5EU and US report that required monitoring programs for infusion and oral DMTs can be a significant issue in comparison to traditional injectable treatments, that can often influence prescribing decisions. Although the perceived monitoring burden is declining over time, further research into how much this monitoring burden impacts HCP prescribing and also patient experience may be beneficial to improving access to these therapies.

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## EP1689

### A Swedish nationwide pharmaco-epidemiological study of the long-term safety and effectiveness of alemtuzumab (IMSE 3)

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**Background:** Alemtuzumab (ALZ) is a modulatory drug for patients with relapsing-remitting multiple sclerosis (RRMS).

Post-marketing surveillance is important to assess the long term safety and effectiveness in a real-world setting. ALZ has therefore been included into the Swedish post-market surveillance study "Immunomodulation and Multiple Sclerosis Epidemiology Study" upon launch in Sweden (March 2014).

**Objective:** To follow up the effectiveness and long-term safety of ALZ in a real-world setting.

**Methods:** Swedish MS patients are registered into the nationwide web-based Swedish neuro registry (neuroreg). Before ALZ initiation, patients are asked to participate in the IMSE 3 study. Adverse events (AEs) and clinical measures; extended disability status scale (EDSS), multiple sclerosis severity scale (MSSS), symbol digit modalities test (SDMT), multiple sclerosis impact scale (MSIS-29), European quality of life - 5 dimension test (EQ-5D), are obtained from neuroreg. The Wilcoxon signed-rank test was used to assess changes in effectiveness.

**Results:** Between March 2014 and April 2017, 104 patients (63% female; 95% RRMS) were included in the IMSE 3 study. Mean age at treatment start was 34 years. Mean number of drugs used before ALZ was 2.8 and most patients switched from Natalizumab (NTZ) (39%). In patients treated with Fingolimod (FGL) before ALZ (n=15), 47% were temporarily ( $\leq 5$  months) treated with NTZ between FGL and ALZ start. 15% had ALZ as their very first disease modifying treatment. Six patients had discontinued ALZ treatment, of which five patients switched to another disease modifying therapy, and one patient died in association with the first ALZ treatment cycle due to fulminant viral hepatitis (Cytomegalovirus, Epstein-Barr Virus). 17 AEs were reported to the Swedish Medical Products Agency, 12 events were classified as non-serious. 97 patients had been treated for at least 12 months and 87 patients for at least 24 months. In patients treated at least 12 months significant improvements were seen for EDSS ( $2.10 \pm 1.57 - 1.67 \pm 1.54$ , n=55), MSSS ( $3.43 \pm 2.76 - 2.64 \pm 2.42$ , n=47), VAS ( $66.8 \pm 21.9 - 73.2 \pm 17.7$ , n=63) and EQ5D ( $0.67 \pm 0.30 - 0.76 \pm 0.25$ , n=70).

**Conclusions:** Neuroreg proves to function well as a post-marketing drug surveillance platform, providing data regarding drug effectiveness and AEs. A longer follow-up period is needed to assess the real-world effectiveness and safety of ALZ.

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#### EP1691

##### A 8-year retrospective cohort study comparing Interferon- $\beta$ formulations for relapsing-remitting multiple sclerosis

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**Objective:** Interferon- $\beta$  has been approved for the treatment of relapsing-remitting (RR) multiple sclerosis (MS), whereas its efficacy in preventing long-term disability and conversion to secondary progressive (SP) MS is still debated. We aim to compare the long-term clinical evolution of newly-diagnosed RRMS patients treated with different Interferon- $\beta$  formulations.

**Methods:** 507 patients were included in the analysis and followed-up for  $8.5 \pm 3.9$  years. 37.6% were treated with subcutaneous Interferon- $\beta$ 1a (Interferon- $\beta$ 1a 44mcg), 33.4% with intramuscular Interferon- $\beta$ 1a (Interferon- $\beta$ 1a 30mcg), and 29.0% with subcutaneous Interferon- $\beta$ 1b (Interferon- $\beta$ 1b 250mcg). Relapse occurrence, 1-point EDSS progression, reaching of EDSS 4.0 and conversion to SP were recorded as outcome measures. To reduce the selection bias, we calculated the propensity score of receiving the specific treatment considering age ( $32.7 \pm 8.3$  years), gender (female 63.1%), disease duration ( $2.7 \pm 2.8$  years), and baseline EDSS (1.5, range 1.0-3.5). Propensity score and covariates (age, gender, disease duration and EDSS) were included in the statistical models.

**Results:** At Cox regression models, the reaching of EDSS 4.0 was 20% higher for Interferon- $\beta$ 1b 250mcg (HR=1.207;  $p=0.063$ ), and 30% higher for Interferon- $\beta$ 1a 30mcg (HR=1.363;  $p=0.095$ ),

when compared with Interferon- $\beta$ 1a 44mcg. The rate of SP conversion was 100% higher for Interferon- $\beta$ 1b 250mcg (HR=2.054;  $p=0.042$ ), and 80% higher for Interferon- $\beta$ 1a 30mcg (HR=1.884;  $p=0.081$ ), when compared with Interferon- $\beta$ 1a 44mcg.

**Conclusion:** Patients treated with Interferon- $\beta$ 1a 44mcg presented with a marginally reduced risk of disability accrual in the long-term, when compared with Interferon- $\beta$ 1b 250mcg and, at least in part, with Interferon- $\beta$ 1a 30mcg. Formulation, frequency of administration and dose of Interferon- $\beta$  might affect the long-term clinical evolution of RRMS.

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#### EP1692

##### Adherence, cognition and behavioral performance in relapsing-remitting MS (RRMS) patients using the electronic auto-injector RebiSmart: 1 and 2 year follow-up from the German multicenter RebiSmart study

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**Background and aims:** Adherence is crucial for therapeutic success in chronic diseases. The electronic autoinjector RebiSmart™ is a unique device allowing objective assessment of interferon (IFN)- $\beta$ 1a sc administration. Our study investigated adherence pattern and cognitive-behavioral variables in RRMS patients using this device.

**Methods:** Prospective, 24-month, non-interventional, multicentre study assessing quantitative (percentage of administered relative to prescribed injections) and qualitative adherence (percentage of weeks with three evenly-timed injections) in RRMS patients (18-65 yr) at months 3/6/12/18/24 after baseline (BL). EDSS, clinical self-rating/NRS, quality of life/MusiQoL, fatigue/FSMC, depression/BDI, information processing/SDMT and word fluency/RWT were assessed at months 3/6/12/18/24 and at BL. 188 patients entered the study (intent-to-treat group/ITT), 129 provided complete adherence data over 12 months (per-protocol study group1 ST1) and 62 over 24 months (ST2). 42 discontinued therapy within 12 month, another 50 within 2nd year, 34 without clear data. 67/188 patients entered an additional support program of the Europa Apotheek Venlo (EAV).

**Results:** In ST1-group quantitative and qualitative adherence was 96,3% and 88,9%, respectively, and in ST2-group 93,4 and 84,6%. 82% of patients in ST1 and 74% in ST2 reached qualitative adherence of at least 80%. Adherence did not significantly differ in the EAV-group. EDSS, NRS, QoL, depression and cognition (verbal fluency, SDMT) remained stable within normal ranges throughout the observation period. FSMC motor and cognitive score increased by 9.4% and 10.0%, respectively, across 12 months (ST1:  $p < 0.002$ ;  $p < 0.035$ ), and only cognitive fatigue by 8,4% ( $p < 0,038$ ) in the ST2 group. ANCOVA indexed fatigue at baseline as a significant predictor of fatigue increase, but not the factors sex, premedication, age, disease duration or EDSS. Dropout analysis revealed no significant differences between adherent and non-adherent patients; dropout in the EAV-group was non significantly lower than that in non-EAVs. Possible predictors of non-adherence will be validated.

#### Conclusion:

- (1) Autoinjector RebiSmart™ proves high adherence for injectable DMTs in RRMS patients.
- (2) High adherence results in stable clinical, cognitive and behavioral parameters.
- (3) Causes of fatigue increase are to be further explored.
- (4) Findings might indicate an advantage of a support-programm concerning persistence.

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#### EP1693

##### Real-world changes in immunological and routine lab parameters of multiple sclerosis patients in 72 months long-term follow up

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**Background:** Natalizumab (NAT) prevents the transmigration of immune cells across the blood-brain barrier thus inhibiting CNS inflammation.

**Objectives:** In this study we present real world laboratory data of 123 NAT treated patients up to 72 months follow up.

**Methods:** 123 patients diagnosed with relapsing-remitting multiple sclerosis (RRMS) and highly active disease course were included. Monitoring of distinct lymphocyte subtypes and standardized lab testing were realized before and every third infusion in 72 months' follow-up. Generalized linear mixed models were used to assess the significance of the results.

**Results:** At every evaluation the lymphocyte count during NAT therapy was significantly higher compared to baseline for all patients (on average 1,8-fold,  $p < 0,001$ ). Although 31% of patients presented lymphocyte count lower than normal limit at treatment initiation, lymphocytes count increased higher than the reference range in 14 % of the patients 6 months after start of NAT. B cells, T cells and NK cells increased significantly (2.6-, 1.6- and 2.0-fold, each  $p < 0,01$ ) after three months and remained stable up to 72 months follow up. Within CD3+ T cells the increase upper normal limit was primarily evoked by CD8+ T cells (increase about 1.8 fold,  $p < 0.01$ ) whereas CD4+ T cells varied in normal range (increase about 1,5- fold,  $p < 0,01$ ). No significant changes were detectable in CD4+/CD8+ ratio, neutrophils or in routine complete blood count. No changes were detectable in serological parameters including creatinine, CRP or liver enzymes.

**Conclusions:** In order to improve decision-making and thus to optimize treatment management long-term monitoring of real world data is notably important. In our present report we observed no relevant immunological effects accompanied with the changes in peripheral immune cell subtypes or standard lab testing of NAT treatment in a 72 months' long-term follow-up.

#### Disclosure

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#### EP1694

##### Hands on experience in therapy management and challenges addressed in an individualized patient support program of three different therapeutic disease-modifying approaches to treat multiple sclerosis in Germany

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<sup>1</sup>Konzept Pharma Service GmbH, Elze, <sup>2</sup>Biogen GmbH, Ismaning, <sup>3</sup>Juliussspital, Würzburg, Germany

**Background:** The complex nature of Multiple Sclerosis (MS) creates a need for different therapeutic options. The oral delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) reduces inflammation and oxidative stress, peginterferon beta-1a (PEG) optimizes interferon-related signaling by reduced injection interval and daclizumab beta (DAC BETA) modulates interleukin-2 signaling by blocking CD25. In addition to MS related adherence barriers, each therapy is accompanied by different challenges based on application route and side effects. Patient support programs (PSPs) optimized for each therapy were thus developed. The objective of this retrospective cohort study is to evaluate the real-life situation for MS patients. Furthermore, the potential benefit of individual patient coaching is analysed.

**Methods:** From February 2014, September 2014 and August 2016 patients were recruited for DMF, PEG and DAC BETA, respectively. All patients signed a written consent form and were provided with a smartphone application with reminder function.

Contents and coaching frequency were adapted according to challenges and patient needs.

**Results:** As of April 2017, 16480 patients were recruited. Data for 9561 and 4619 MS patients including 1472 and 1142 dropouts could be analyzed for DMF and PEG, respectively. Overall, gastrointestinal issues (GI) (24.6%) for DMF and flu-like symptoms (FLS) (36.6%) for PEG were reported as the most frequent drop-out reason of the discontinuers. While GI was most frequent in the first three therapy months, FLS were consistently the main reason for PEG therapy discontinuation. Time to therapy discontinuation was differentiated for more intensively and less intensively coached patients. 5.9%, 10.4% and 18.0% of more intensively coached DMF patients stopped therapy after 3, 6, and 12 months compared to 10.4%, 15.9% and 25.3%, respectively. PEG therapy discontinuation after 6 months was reduced for more intensively coached patients by 4.1% ( $p=0.0003$ ) compared to the less intensively coached group. The preliminary result for DAC BETA therapy discontinuation after 6 months is 4.3% ( $n=139$ , 6 dropouts).

**Conclusion:** Side effects reported in the phase III studies are the main reasons for discontinuing MS therapy. Patient coaching provides an essential contribution effectively address preventable or manageable side effects and promotes regular treatment monitoring, leading to supervised therapy continuation and treatment satisfaction.

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## EP1695

### Effectiveness and safety of long-term fingolimod treatment in relapsing-remitting multiple sclerosis patients with highly active disease

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**Background:** Fingolimod treatment improved the clinical and MRI outcomes over 12 months in relapsing-remitting MS (RRMS) patients with highly active disease (H<sub>AD</sub>) after an exposure to previous disease-modifying therapies (DMTs)<sup>1</sup>.

**Objective:** To evaluate the long-term effectiveness and safety of fingolimod in RRMS patients with H<sub>AD</sub> after an exposure to previous DMTs.

**Methods:** LONGTERMS is a single-arm, open-label extension study of phase 2/3 trials of fingolimod in relapsing MS. Two cohorts of patients who received fingolimod 0.5 mg as the only dose in the core phase of three phase 3 trials were analysed: Highly active disease cohort (H<sub>AD</sub>C, N=463) and overall core cohort (CC, N=1212). H<sub>AD</sub>C included patients who received any DMT during the year before study entry and either (1) had as many or more relapses in the year before study entry than 2 years before study entry or (2) had  $\geq 1$  relapse in the previous year and  $\geq 1$  Gd+ T1 lesion or  $\geq 9$  T2 lesions at baseline (BL). Effectiveness evaluations included relapse (annualised relapse rate [ARR], estimated by negative binomial regression) and disability outcomes (Kaplan-Meier [KM] estimates for patients not reaching Expanded Disability Status Scale (EDSS) of  $\geq 4$ ,  $\geq 6$ , or  $\geq 7$ ). Incidence rate ratios (IRRs; IR for H<sub>AD</sub>C/CC) were reported for any adverse events (AEs) and serious AEs (SAEs).

**Results:** BL demographics and disease characteristics of patients in the H<sub>AD</sub>C and CC cohorts were: women, 74% and 70%; mean age (years), 38.6 and 37.9; mean number of relapses in the year prior to enrolment in the core studies, 1.5 and 1.5; mean EDSS, 2.5 and 2.3. The median (range) exposure to fingolimod was: H<sub>AD</sub>C, 1361 (2-3546) days and CC, 1545 (2-3619) days. From BL to Month (M)<sub>120</sub>, 46% and 53% of patients remained relapse free in the H<sub>AD</sub>C and CC, respectively. The ARR (95% CI) remained low during M<sub>0-6</sub> to M<sub>0-120</sub> (H<sub>AD</sub>C, 0.46 [0.38; 0.56] to 0.27 [0.24; 0.31]; CC, 0.36 [0.32; 0.41] to 0.21 [0.19; 0.23]). At M<sub>96</sub>, most patients in both H<sub>AD</sub>C and CC did not reach an EDSS score of  $\geq 4$  (64% and 71%),  $\geq 6$  (83% and 86%) or  $\geq 7$  (98% and 97%). The IRs for any AE or SAE were higher in the H<sub>AD</sub>C vs CC: IRR (95% CI) for AEs was 1.37 (1.23; 1.53) and SAEs was 1.26 (1.02; 1.54).

**Conclusions:** For patients remaining on long-term fingolimod treatment, those with H<sub>AD</sub> after an exposure to previous DMTs showed benefits in terms of low ARR, delayed EDSS progression and no new safety concerns. The intrinsic limitation of the open-label extension study cannot be excluded.

## Disclosure

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#### EP1696

##### Interim data from the Hungarian fingolimod registry (CFTY720DHU01)

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**Background:** Fingolimod is a sphingosine 1-phosphate receptor modulator approved by the European Medicines Agency (EMA) in 2011. Fingolimod has been reimbursed in Hungary since 2014 for second-line and for first-line treatment of patients (by reference to the summary of product characteristics ) with relapsing-remitting multiple sclerosis (RRMS) to reduce disease activity.

**Objective:** This non-interventional study aims to collect long term data on real-world effectiveness in patients treated with fingolimod in Hungary.

**Design and methods:** This study combines retrospective and prospective methods from fingolimod treated patients in order to obtain long term 5 year datasets from 21 multiple sclerosis centers. The interim analysis on the dataset was available on 31 October 2016.

**Results:** 475 patients were entered in the registry until 31 October 2016; 70% of patients were female. The mean disease duration of total patients is 10.56±6.69 years. 92.10% patients were treated with previous immunomodulatory therapy. 276 (58.10 %) and 177 (37.26 %) patients had received fingolimod for at least 1 or 2 years, respectively. The annual relapse rate (ARR) of patients treated with fingolimod was substantially reduced from 0.90±0.75 (baseline) to 0.21±0.55 (p< 0.001) during the first year of treatment and to 0.36±0.69 (p< 0.001) by the end of the second year. The mean baseline Expanded Disability Status Scale (EDSS) score was 2.82±1.58 at baseline. The EDSS score did not change substantially over time, by the end of the first year the mean score was 2.84±1.68 (p=0.423), by the end of the second year it was 2.97±1.80 (p=0.423).

**Conclusions:** The results of the 2 year interim analysis of Hungarian fingolimod registry support the positive effectiveness profile of fingolimod demonstrated in phase III clinical trials with real world evidence data.

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## EP1697

**Long-term safety profile of fingolimod in the treatment of multiple sclerosis: Results of the 'DIAMOND' non-interventional, prospective, observational study conducted in the routine care of Greece**

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**Background:** This study aimed to further characterise the safety profile of fingolimod, the first approved oral therapy for multiple sclerosis (MS), by generating real-world evidence on its long-term (2-year) safety.

**Methods:** A total of 506 patients (498 eligible) were enrolled in this non-interventional, observational study between 20-Feb-2012 and 13-Jan-2014 at 40 study sites across Greece. Patients were followed over a period of 24 months. Fingolimod (0.5 mg) had been initiated 0 to 15 days prior to enrolment (median: 0.0 days).

**Results:** Over a median of 23.6 months of fingolimod exposure, 20.5% (n=102) patients experienced 233 fingolimod-related adverse events (AECOMMON AEs (i.e. frequency  $\geq 1\%$ ) included 'lymphopenia' [45 events by 8.8%; exposure-adjusted incidence rate (EAIR): 5.3 cases per 100 patient-years; 95%CI: 3.8-7.1]; 'leukopenia' (21 events by 4.2%; EAIR: 2.4; 95%CI: 1.5-3.7); 'hepatic enzyme increased' (31 events by 3.4%; EAIR: 2.0; 95%CI: 1.1-3.1), 'headache' (9 events by 1.8%; EAIR: 1.0; 95%CI: 0.5-2.0); 'dizziness' (7 events by 1.2%; EAIR: 0.7; 95%CI: 0.3-1.5), 'bradycardia' [6 events (five on the day of fingolimod onset) by 1.2%; EAIR: 0.7; 95%CI: 0.3-1.5]; and 'herpes viral infections' (5 events by 1.0%; EAIR: 0.6; 95%CI: 0.2-1.3). Overall, infections (19 AEs) were reported by 3.0% (EAIR: 1.7; 95%CI: 1.0-2.8) of the patients. Among other events of interest, malignant neoplasms (one event each of B-cell lymphoma and intestinal adenocarcinoma) were reported in 0.4%, while there was a single event of a first degree atrioventricular block. Serious AEs were reported by 9.6%; 'lymphopenia' (5.0%; EAIR: 2.9; 95%CI: 1.9-4.3), 'leukopenia' (1.6%; EAIR: 0.9; 95%CI: 0.4-1.8), and 'hepatic enzyme increased' (1.4%; EAIR: 0.8; 95%CI: 0.3-1.6) were the only common serious AEs. No cases of macular oedema were reported. Overall, 5.6% of the patients permanently discontinued fingolimod treatment due to AE occurrence. At the end of the study, 57.1% of the AEs had recovered, 32.6% were ongoing, 8.2% had fatal outcome, while the outcome was unknown in 2.1%.

**Conclusions:** The study yielded real-world data on the well-established safety profile of fingolimod in a representative MS population. No new safety signals were identified.

**Disclosure**

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All authors, except of E.Z are Principal Investigators of the study.

## EP1698

**Discontinuation of dimethyl fumarate in relapsing multiple sclerosis in a single centre**

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**Introduction:** Dimethyl fumarate (DMF) is an oral disease modifying therapy (DMT) licensed to treat relapsing multiple sclerosis (RMS). The rate of discontinuation due to adverse effects in the pivotal trials was 12-16%. We aimed to determine the stopping rate at Imperial College Healthcare NHS Trust (ICHNT) and the reasons for its discontinuation.

**Method:** Patients who discontinued DMF were identified from a local database. These patients were interviewed using a telephone questionnaire. The reasons for stopping treatment were recorded. Patients who had stopped due to side effects were asked to identify which health care professional they had contacted prior to this decision. Information on subsequent treatment choices was also obtained.

**Results:** ICHNT recorded 352 patients being treated with DMF. 142 (29%) patients were identified as having stopped treatment. Excluding those stopping for progression the discontinuation rate was 20%.

39 patients (28%) stopped due to disease progression, 14 patients (10%) due to lymphopenia, and 55 patients (39%) due to side effects, with the remaining 33 (23%) stopping for a range of other reasons.

The peak period for discontinuation due to side effects was 3-5 weeks after starting treatment. Discontinuation due to lymphopenia peaked at 7-12 months, and for disease progression was after more than 1 year on treatment. 73% of patients who experienced

side effects were offered an alternative drug. 17% were given a temporary dose reduction. The majority of patients discussed their side effects with either their neurologist or their MS nurse. 26% of patients stopped with no discussion with a health care professional.

**Conclusion:** This real world data shows the rate of discontinuation of DMF due to side effects to be greater than that reported in clinical trials. A significant number of patients are stopping treatment with DMF due to side effects and being switched to alternative therapy. This has implications both for the patient & the MS service. By identifying the peak time for discontinuation due to side effects the MS team can target follow up with these patients at 2 weeks & offer telephone counselling from an appropriately trained pharmacist or MS nurse to improve management of side effects & adherence to therapy.

### Disclosure

Esfahani Motlagh B Nothing to declare

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### EP1699

**Retrospective longitudinal analysis of cognition and clinical-behavioral parameters (PRO) in relapsing-remitting multiple sclerosis (RRMS) patients treated with Teriflunomide - results from a 12 month registry study in German practice centers**

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**Background:** There is limited experience about how the new oral MS drugs influence non-motor symptoms of MS and cognition over time, especially under real-life conditions.

**Objectives:** To longitudinally assess

(1) the evolution of cognition, course and PROs in RRMS patients on teriflunomide as first-line therapy (de novo) or changing from other MS therapies (switchers)

(2) outcomes between de novos and switchers,

(3) differences in re-test effects between RRMS and controls.

**Methods:** Retrospective, multicenter, open-label registry data analysis of 35 German MS practices (NTD network) with respect to teriflunomide therapy in RRMS. Data were available at baseline (T0) and after 12 months (T12) identifying 246 RRMS patients on teriflunomide (Mc Donald; mean age: 45.8 yr, 67.5% female, mean EDSS 2.2) having completed a 12-month treatment

period. Among them were 81 (32,9%) de-novos and 165 (67,1%) switchers.

**Outcomes:** clinical status, EDSS, IQ (MWT-B), cognition indexed by information processing, verbal and visuo-spatial memory (SDMT, CVLT, BVMT-R) from BICAMS battery, (2) interference control (Stroop), (3) fluency (RWT), and PROs represented by motor and cognitive fatigue (FSMC), depression (BDI, fast screen) and QoL (EQ-5D).

**Results:** At baseline (T0), RRMS patients performed below normal controls in most cognitive tests. Motor fatigue scored at a medium, cognitive fatigue at a low level, depression in the normal range. Across time (T12 vs. T0), 86,4% of patients remained relapse-free and EDSS stable (2.3 vs. 2.2), as did BICAMS parameters (SDMT, CVLT, BVMT-R) and 3 dimensions of fluency, i.e. semantic, formal-lexical and semantic category change (RWTsf, RWTflcc, RWTscc). Significant cognitive improvement was found for formal-lexical word fluency (RWTflw: 17.7 vs. 19.7,  $p < .000$ ) and interference processing (2 Stroop runs;  $p < 0.03$ ,  $p < 0.04$ ). Depression scored normal (2.5 vs. 2.7). Motor FSMC subscore persisted at medium level (29.4) whereas cognitive fatigue augmented significantly (25.8 vs. 27.1,  $p < 0.049$ ). Outcomes were not significantly different between de novo and switchers. Cognitive evolution was less positive, but insignificantly different, in RRMS vs. controls.

### Conclusion:

- (1) Teriflunomide is effective stabilizing or improving cognition and most clinical-behavioral outcomes in RRMS.
- (2) Switchers take comparable benefit from therapy as de novo patients
- (3) Positive cognitive dynamics around re-test effects is less expressed in RRMS patients than controls.

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### EP1700

**The inclusion of cognitive evaluation into NEDA-3 (NEDA-3/Co) further confirms the high efficacy of natalizumab in multiple sclerosis**

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**Background:** Natalizumab (NTZ) has proved to be highly effective in MS, arresting inflammation and improving clinical outcomes. However, its effect on cognition has been poorly investigated.

**Aim of the study:** To evaluate the efficacy of natalizumab (NTZ) by incorporating cognitive outcomes (Co) into NEDA (no evidence of disease activity)-3 criteria (NEDA-3/Co). To evaluate at therapy initiation the presence of clinical and neuropsychological parameters that may influence NTZ efficacy.



**Methods:** NTZ-treated patients were enrolled in a two-year longitudinal study. At therapy initiation, brain MRI, neurological examination by means of the expanded disability status scale (EDSS) and neuropsychological assessment by means of the Brief Repeatable Battery of Neuropsychological Tests (BRB-NT) were performed. Thereafter, EDSS evaluation was performed every 6 months, brain MRI every year and neuropsychological assessment at the end of the follow-up. NEDA-3 was evaluated at the end of follow up and was defined as no evidence of clinical activity (i.e., no relapse and no increase in EDSS= *clinically silent patient*, CS) and no evidence of MRI activity (i.e., no evidence of new/enlarging T2 lesions, no evidence of gadolinium enhancing lesions= *MRI silent patient*, MRIS). MS patients with no evidence of cognitive decline (no evidence of cognitive impairment in at least one further item) at year 2 were defined as neuropsychological silent (*cognitive silent*, CoS) patients.

**Results:** On May 2017, 123 patients concluded the two-year follow-up: 83% were CS, 80% were CoS and 73% were MRIS. 77 patients (63%) were NEDA-3, and 80.5% of these (62 patients= 50% of the total number) were also NEDA-3/Co. CS, MRIS, CoS and NEDA-3 percentages did not differ between treatment-naïve and previously-treated patients. CoS rates did not matched to CS or MRIS rates. No clinical parameter at baseline was found to predicted NEDA-3/Co. However, normal Word List Generation test at therapy initiation was mildly associated to a higher probability of NEDA-3/Co (OR 4.95, IC<sub>95%</sub> 1.3-18.8,  $p < 0.05$ ).

**Conclusion:** The inclusion of cognitive evaluation into NEDA-3 further proved the high efficacy of NTZ in MS patients. Since cognitive decline in MS is mainly related to cortical grey matter damage, the incorporation of cognitive impairment into NEDA-3 may help to monitor the effect of therapies on the neurodegenerative component of MS.

## Disclosure

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## EP1701

### Real-world evidence of patients treated with alemtuzumab in Canada

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**Background:** Alemtuzumab is approved in Canada for the treatment of adult patients with RRMS with active disease as defined by clinical and imaging features, and an inadequate response to interferon- $\beta$  or other disease-modifying therapies (DMTs). In the CARE-MS II study (NCT00548405), alemtuzumab (12 mg/day IV; 5 consecutive days at baseline, 3 consecutive days 12 months later) significantly improved clinical and MRI outcomes vs SC IFNB-1a (44  $\mu$ g; 3 times weekly) in patients with active RRMS who had an inadequate response to prior therapy.

**Goal:** To describe real-world evidence (RWE) demographic and clinical characteristics of patients treated with alemtuzumab in clinical practice in Canada relative to the CARE-MS II study population.

**Methods:** MS One-to-One is a patient support program for patients with RRMS, facilitating access to alemtuzumab and ensuring monitoring during treatment. In this retrospective, descriptive analysis, demographic and clinical characteristics of real-world Canadian patients, who were previously treated with other DMT(s) and who received alemtuzumab between 1 Jan 2014 and 1 May 2017, were assessed and compared with baseline characteristics of patients who participated in CARE-MS II. Consent was provided by neurologists and patients for the use of all clinical information from MS One-to-One.

**Results:** A total of 494 patients were enrolled in the Canadian MS One-to-One program and had received at least 1 course of alemtuzumab and  $\geq 1$  prior DMT. Of these, 33.0% had been treated with 1 prior DMT, 30.2% had 2 prior DMTs, and 36.8% had  $>2$  prior DMTs. The majority of patients were switched from either fingolimod (32.6%), dimethyl fumarate (22.5%), natalizumab (19.8%), or glatiramer acetate (13.4%). Reasons for switching included lack of effectiveness (45.7%), tolerability (17.2%), and physician choice (7.5%). In comparison to the CARE-MS II population at study baseline, the Canadian real-world alemtuzumab-treated patient population was older (38.9 years [y] vs 34.8 y), included a greater percentage of females (74% vs 66%), had a longer duration of disease (8.0 y vs 4.5 y), and had a similar mean EDSS score at baseline (3.0 vs 2.7).

**Conclusion:** This analysis represents RWE of previously treated patients receiving alemtuzumab in Canada. As RWE is gained, the use and sequencing of alemtuzumab may evolve.

**Study support:** Sanofi.

## Disclosure

AS, LH, EP, and AG: Employees of Sanofi.

## EP1702

### Illness- and medication-perceptions are key predictors of adherence in patients with MS

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**Background:** Adherence to medication is the extent to which a patient acts in accordance with the prescribed interval and dose of a medication regimen. Adherence comprises of implementation and persistence of habit and is estimated to be around 50% in chronic illnesses as MS. Existing evidence indicates that improved medication adherence could have a major effect on disease progression and overall health in patients with MS. There's scarce knowledge about perception- related aspects as predictors of non-adherence to medications among people with Multiple Sclerosis (PwMS).

**Aim:** To identify prospective indicators of non-adherence to medication in MS.

**Methods:** Participants were 96 relapsing-remitting PwMS treated at our MS Center. Questionnaires assessing adherence, demographic data, illness and medicine perceptions, health-related quality of life (HRQoL), habits, and emotional factors were filled by participants. Physical disability (EDSS) was evaluated by the treating neurologist. The questionnaires and physical evaluation were administered at baseline and 6 months later. Adherence was defined using the Probabilistic Medication Adherence Scale (ProMAS) and participants were divided to 2 levels of adherence.. Univariate analysis was conducted to assess the association between background, perceptual and medical variables with adherence.

**Results:** Participants' adherence rates were divided into 2 subgroups: 67 (69.8%) participants reported high adherence and 29 (30.2%) reported medium-low adherence.

Pearson correlations indicated that illness- and medications-perceptions are key predictors of adherence 6 months later. The 5 predictors were:

Illness perception, understanding the illness, (OR=3.062, p=0.045); Health perception (OR=6.667, p=0.012); Satisfaction with care (OR=5.25, p=0.012); Medication perception -overuse (OR=3.422, p=0.011); Medication perception -harm (OR=3.030, p=0.009).

Demographic data, physical disability status, HRQoL, habits, depression and anxiety had no significant predictive value.

**Conclusions:** Our study suggests that illness- and medication-perceptions, malleable constructs, are key predictors of adherence among PwMS. Interventions should be developed to improve medication adherence among these subgroups so that patients can achieve the full benefits of prescribed pharmaco-therapies.

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## EP1703

### The 20-year history: change of multiple sclerosis patient profile over 20 years

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The first disease modifying treatment (DMT) option for multiple sclerosis (MS) was started to be used at the end of 1996, in Turkey. The aim of this study was to investigate the effect of the development of treatment options on the MS patient profile, comparing 1996, when no DMT was available, and 2016, when almost every treatment options were available.

This study was conducted retrospectively examining the patient records of Dokuz Eylul MS Clinic. The patient records (all clinic days throughout the year) in 1996 were compared to those in 2016. Patients who applied to the clinic for routine control, and having a clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), or primary progressive MS (PPMS) were included. Patients applied to the clinic for a suspected relapse were excluded.

The records including 1929 visits in 1996 were compared to 2245 visits in 2016. The mean frequency of visits were significantly higher in 1996 compared to 2016 (once in 3.7 vs. 5.8 months, p=0.003). No significant difference was found in age and disease duration of the patients visited in 1996 and 2016. There were significantly more number of patients with clinically isolated syndrome (8.2 vs. 3.6%, p=0.004) and SPMS (36.3 vs. 21.4%, p< 0.001) in 1996; however, significantly less number of patients with RRMS (51.4 vs. 70.4%, p< 0.001). The number of patients with the Expanded Disability Status Scale (EDSS) scores of ≤3 were significantly higher in 2016 (68.7 vs. 44.5%, p< 0.001). On the other hand, the number of patients with the EDSS scores of 6-6.5 and ≥7 were significantly less in 2016

(9.2 vs. 21.0% and 3.7 vs. 12.8%, respectively, p< 0.001). Significantly more patients with SPMS, EDSS scores of 6-6.5 and ≥7 (wheel-chair dependent patients) came to the clinic in 1996 compared to 2016 (14.3 vs. 10.0%, 0.006; 8.4 vs. 4.3%, p< 0.001; 5.1 vs. 1.7%, p< 0.001, respectively).

The emergence of treatment options in MS and the increasing availability of new treatment options for patients with no/inadequate treatment response have changed the MS patient profile over the 20 years. The proportion of patients with SPMS and higher EDSS scores reduced. Thus, the number of wheelchair-dependent patients also dramatically reduced. The reduction in the proportion of patients diagnosed with clinically isolated syndrome seems to

be related to the narrowing of the clinical definition of clinically isolated syndrome with new diagnostic criteria.

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### EP1704

#### Safety and efficacy of long-term treatment with daclizumab beta: 6-year results from the SELECTED extension study

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<sup>10</sup>Biogen, Maidenhead, United Kingdom, <sup>11</sup>Biogen, Cambridge, MA, United States

**Background:** SELECTED (NCT01051349) was an open-label extension study that evaluated treatment with daclizumab beta (DAC BETA) for up to 6 additional years in patients with relapsing MS (RMS) who completed the randomized SELECT/SELECTION studies. A previous interim analysis of SELECTED showed that efficacy was maintained over 3 years of continuous treatment and adverse events (AEs) did not increase over time.

**Objective:** To report the long-term safety and efficacy outcomes in RMS patients treated with DAC BETA in SELECTED.

**Methods:** Patients who completed 1-2 years of treatment with DAC BETA in SELECT/SELECTION were eligible to receive open-label DAC BETA 150mg subcutaneous every 4 weeks for up to 6 more years in SELECTED. To consolidate extension studies, SELECTED was stopped early and patients transitioned to the open-label EXTEND (NCT01797965) study that also includes patients from DECIDE and OBSERVE.

**Results:** 90% (410/455) of patients who completed treatment in SELECT/SELECTION enrolled in SELECTED. The mean (median) time on treatment in SELECTED was 40.2 (45.1; range:0-66) months; 69% of patients received DAC BETA for >3 years, 39% for >4 years and 9% for >5 years. The incidence of AEs in Years 1, 2, 3, 4 and ≥5 was 60%, 60%, 57%, 56% and 51%. 87% of patients experienced an AE; 26%, a serious AE excluding MS relapse. Most patients (75%) had AEs that were mild/moderate in severity. There were no deaths during the study. Incidence of alanine transaminase and/or aspartate transaminase elevations >5x upper limit of normal was 9% and 6%, respectively. The adjusted annualised relapse rate (95%CI) in Years 1, 2, 3, 4 and ≥5 was 0.150 (0.111, 0.205), 0.122 (0.087,

0.170), 0.105 (0.074, 0.148), 0.133 (0.084, 0.211) and 0.087 (0.054, 0.140). The incidence of 24-week confirmed disability progression was low (17.4%) with a stable rate of occurrence over the study period. The mean numbers of new Gd<sup>+</sup> and new/newly enlarging T2 hyperintense lesions occurred at rates similar to the reduced rates in SELECT/SELECTION. The percentage change in whole brain volume was -0.4%, -0.4%, -0.2%, -0.5%, -0.2% and 0.1% for Years 1, 2, 3, 4, 5 and 6, respectively.

**Conclusions:** Results from SELECTED extend those from SELECT/SELECTION and together show that the effects of DAC BETA on clinical and radiologic outcomes and the favourable benefit/risk profile of DAC BETA were sustained over up to ~8 years of treatment, with no new safety concerns identified in the SELECTED study population.

### Disclosure

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**R. Robinson:** employee of and holds stock/stock options in AbbVie Inc.



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#### EP1705

##### **Real world lab data: Intra- and inter-individual changes in fingolimod treated MS patients**

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**Background:** As a disease modifying therapy fingolimod (FTY) prevents lymphocytes egress into peripheral blood which results in peripheral lymphopenia. So accurate monitoring of lab data is necessary. In this real world study we analysed laboratory data of 128 FTY treated patients up to 36 months follow up.

**Methods:** 128 patients diagnosed with relapsing-remitting multiple sclerosis and highly active disease course were included. Real world monitoring of lab testing was performed before and every third months up to 36 months' follow-up. Generalized linear mixed models were used to assess the significance of the results.

**Results:** We analyzed peripheral immune cell populations including T, B, NK cells and granulocytes. Leukocyte presented at a significantly lower level compared to baseline in each analysis ( $p < 0,001$ ) and remained stable after the 1st application. After FTY start, leukocytes decreased by approximately 40% during the entire observation period and decreased below 3.8 GPt/L in one-third of the treated patients. Within first month of therapy, lymphocytes declined by about 70%. Within treated patients, 98% presented lymphocyte count  $< 1,5$  GPt/L, 93.7%  $< 1,0$  GPt/L, 55.8%  $< 0.5$  GPt/L and 2.1%  $< 0,2$  GPt/L. During period of observation, levels of leukocyte respective lymphocyte counts fluctuated about 0.8 respectively 0.14 in FTY treated patients. Compared with the intra-individual variability of patients treated with natalizumab (fluctuation leukocytes 1.5 and lymphocytes 0.6), FTY treated patients demonstrated a narrow deviation range and more stable values. No significant changes were detectable in triglycerides, cholesterol, high and low-density lipoprotein. After first application aspartate-aminotransferase (ASAT) levels increased in 25%, alanine-aminotransferase (ALAT) in 22% and  $\gamma$ -glutamyl transferase ( $\gamma$ GT) in 26% of patients higher than upper limit.

**Conclusions:** Although it is widely known that FTY induces lymphopenia, we have shown that as well in the real world the lymphocyte counts decreased in only a small number of patients under a critical limit of 0,2 GPt/L in a real-world cohort. Additionally we present stable levels in lymphocyte count and only small intra- and inter-individual fluctuations in treated patients during long-term follow up evaluation.

#### **Disclosure**

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#### EP1706

##### **Analysis of the effectiveness of natalizumab through non-evidence of disease activity (NEDA-3) criteria in real world practice in a tertiary hospital in Asturias Spain**

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**Introduction:** Natalizumab (NTZ) is used in patients with high active disease or a severe and rapid onset. The efficacy of NTZ has originated the concept of NEDA. The concept of NEDA-3, "no evidence of disease activity" is based on the absence of relapses, progression of disability and activity on MRI. The major limitation for the use of NTZ is the development of progressive multifocal leukoencephalopathy (PML).

**Objectives:** Our objective is to analyze the percentage and the duration over time patients meet NEDA-3 criteria in real world clinical practice in multiple sclerosis (MS) under treatment with NTZ.

**Methods:** We retrospectively reviewed the clinical records of 97 MS patients who have received NTZ therapy for at least one year at the Neurology Service of Hospital Universitario Central de Asturias (Oviedo, Spain) since year 2008 to present.

**Results:** We analyzed 97 patients, 75.3% women, 93.8% with relapsing-remitting MS. The median age of the patients at the beginning of treatment was 41,1 years old. The baseline EDSS was 3.3. The time from diagnosis to the onset of NTZ was 5.84 years. The annualized relapse rate (ARR) in the year prior to treatment was 1,91. The reason for initiating NTZ was the lack of efficacy of prior treatment in 83.5% and 8.24% for an aggressive onset of the disease. The mean treatment time was 4.24 years. At the beginning of treatment 60% of the patients had anti-JCV positive antibodies. 25% of patients with negative anti-JCV antibodies become positive in the course of treatment. In 74.4% the reason for withdrawal of NTZ was the risk of PML.

In the case of NEDA-3 after one year of treatment, 66.7% of the patients fulfilled the criteria, after two years 54.7%, after three 50.7%, after four 44.4%, after five 40.5%, after six 34, 4%, after seven 39.1%, after eight 53.8% and after nine 60%. The ARR reduction was 87.44% that was maintained over the years.

**Conclusion:** NTZ is used in patients with high clinical and MRI activity. In our series, a high percentage of patients treated with NTZ met NEDA-3 criteria and maintained over the years. One of the major limitations of treatment is the risk of PML, which is the most frequent reason for withdrawal.

#### **Disclosure**

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Castañón-Apilánez, M. Nothing to disclose.

Villafani, J. Has received grants as a speaker's from Biogen, TEVA, Genzyme and Novartis

## EP1707

**Six year prospective immunological study of alemtuzumab treated patients: identification of markers of the clinical response**

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**Background:** Alemtuzumab is a highly effective treatment for relapsing remitting multiple sclerosis (RRMS) that selectively targets the CD52 antigen, with consequent profound T and B lymphocyte depletion. In particular alemtuzumab induced a CD4+ T cells lymphopenia, a decrease of Th17 and Th1 cells and pro-inflammatory molecules and a restored Treg suppressor function that long last for years. 25-30% MS patients, however, relapse after alemtuzumab treatment.

**Aims:** Long-term immunological study of RRMS patients after alemtuzumab treatment to identify markers that could help to predict the clinical response to the drug.

**Methods:** Multicenter follow-up of 29 alemtuzumab-treated RRMS patients from 6 European sites in the CARE-MS I and CARE-MS II trials. Patients received two courses of alemtuzumab at Month 0 and 12. Further courses have been repeated in non responders. Clinical and immunological evaluation were performed at Months 0, 6, 12, 18, 24, 36, 48, 60 and 72. CD4+ T cells, Treg, Th1 and Th17 cells were evaluated in the peripheral blood mononuclear cells by FACS analysis. mRNA levels of cytokines, chemokines, chemokine receptors and transcriptional factors with pro-inflammatory (IL-1 $\beta$ , IL-2, IL-6, IL-12, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-26, IFN- $\gamma$ , T-bet, RORC, TNF- $\alpha$ , CCR3, CCR4, CCR5, CCR6, CXCR3, CXCL10, CCL20, VLA4) or anti-inflammatory function (IL-10, IL-27, TGF- $\beta$ , FoxP3) were quantified by TaqMan® low density array real-time polymerase chain reaction in whole blood.

**Results:** Nine patients had a clinical or MRI disease activity resumption between Month 20 and 32. At Month 18 they had a higher Th17/Treg ratio and increased IL-1 $\beta$  mRNA levels compared to patients that remained stable. Two patients continued to present evidence of disease activity despite repeated alemtuzumab courses. They display an atypical CD4+ T population behaviour different from the other patients. Despite that lymphocyte count strongly decreased after the first administration of alemtuzumab and then fluctuated accordingly to alemtuzumab administration, the percentage of CD4+ cells was not or just mildly affected.

**Conclusions:** An increase of Th17/Treg ratio and of the pro-inflammatory cytokine IL-1 $\beta$  mRNA level after alemtuzumab could be an early marker of MS disease activity resumption suggesting alemtuzumab retreatment. Furthermore, the evaluation of the CD4+ cell percentage could represent a helpful tool to address the individual clinical response to the drug.

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SR had travel expenses for congress paid by Sanofi-Genzyme;

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DT: nothing to disclose;

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MC received personal compensation by Merck and Biogen for participating to advisory boards; by Merck for editorial collaborations and had travel expenses for congresses paid by Merck, Biogen, Novartis and Sanofi-Genzyme.

## EP1708

**Adherence to oral versus injectable disease-modifying therapies for multiple sclerosis using French national health insurance databases**

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**Background:** Twelve disease-modifying therapies (DMTs) specific for multiple sclerosis (MS) are now available in France, whom three are oral medications (fingolimod, dimethyl fumarate, teriflunomide).

A higher adherence to oral drugs may be expected compared to injectable ones. To our knowledge, no study has compared adherence in patients who received both types of DMTs over time.

**Objective:** From administrative databases we aimed to compare adherence to DMTs according to their route of administration - oral vs injectable - within a unique group of patients, who switched from injectable to oral drugs.

**Methods:** People with MS were identified between 2011 and 2015 in a random sample of French healthcare insurance system thanks to a three-criterion algorithm using diagnoses of hospital admissions, DMTs and MS long disease duration status. Only patients who went from an injectable to an oral DMT over the study period (2011 to 2015) were selected (all duration between the two DMTs were considered). Adherence was estimated using the medical possession ratio (MPR), a threshold of  $\geq 0.8$  being

considered as optimal adherence. For each DMT it was calculated from the date of first dispensation (index date) to either estimated end of treatment or the end of follow-up on 31st December 2015. Differences between injectable and oral DMTs regarding MPR and proportion of optimal adherence were tested with a paired sign rank test and a McNemar's test respectively.

**Results:** A switch from an injectable to an oral DMT was identified for 100 out of 1,153 patients with MS. Median age was 45 years and 67% were female. Median treatment duration was 846.5 and 296.0 days for injectable and oral DMTs respectively. Mean MPR was higher for oral compared to injectable DMTs (0.97 vs 0.89,  $p < 0.001$ ). The proportion of optimal adherence differed significantly between oral and injectable (93% vs 76%,  $p < 0.001$ ). Results were consistent when selecting a minimum of 6-month DMTs duration (97% vs 75%,  $p < 0.001$ ).

**Conclusion:** In patients who switched from injectable to oral DMTs, we found higher adherence for oral DMTs than injectable ones. It may reveal that reason for switching was lack of adherence or injections' weariness. However, high adherence to oral DMTs may also be linked to the limited treatment duration and may decrease over time. We plan to assess adherence also in non-switchers (only oral or only injectable), and for each DMT separately. Comprehensive results will be available in October 2017.

## Disclosure

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Alice Guilleux has no disclosure to report.

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## EP1709

### Long-term effectiveness of fingolimod in multiple sclerosis patients treated in the routine care of Greece: results of the 'DIAMOND' non-interventional, prospective, observational study

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**Background:** This non-interventional, prospective observational study aimed to provide real-world data to complement pre-authorization evidence on fingolimod's effectiveness in relapse rate, disability progression and MRI measures in multiple sclerosis (MS) patients.

**Methods:** 498 adult MS patients, who had recent (up to 15 days) treatment initiation with, or had been prescribed fingolimod, according to the approved label prior to enrolment, comprised the eligible study population. Data were collected over a median follow-up of 23.6 months, during 7 visits occurring at enrolment and at approximately 1, 3, 6, 12, 18 and 24 months post-enrolment. 25.3% of the patients prematurely discontinued study participation at a median of 12.8 months, mainly due to loss of follow-up (9.0%), adverse events (6.8%), and patient decision/non-compliance/consent withdrawal (4.6%).

**Results:** Eligible patients (age: 41.2±9.8 years; 63.7% females) had been diagnosed with MS a median of 7.5 years prior to fingolimod onset. All patients had experienced at least one relapse over 12 months prior to treatment onset [total 803 (mean: 1.6±0.8); 675 treated with corticosteroids]. 95.8% of patients had received prior MS-related treatment; 73.8% of these patients had discontinued their most recent prior medication within the 6-month period prior to fingolimod treatment onset. The median baseline EDSS score of 3.2±1.9 significantly decreased to 3.1±1.9 ( $p < 0.001$ ), 3.0±1.9 ( $p = 0.003$ ), 3.1±1.9 ( $p = 0.020$ ) and 3.0±1.9 ( $p = 0.010$ ) point at 6, 12, 18 and 24 months post-treatment, respectively. Brain MRI among patients with available data demonstrated significant decreases from baseline in gadolinium-enhancing lesion count at 6, 12, 18 and 24 months ( $p < 0.001$  for all) and in T1 lesion count at 12 ( $p = 0.006$ ) and 24 months ( $p = 0.046$ ), while the T2 lesion counts remained unchanged. The 12- and 24-month annualised relapse rates were 1.81 and 1.85 per patient-year, respectively, prior to fingolimod onset, and 0.10, and 0.09, respectively, post-treatment onset. Median decreases of 1 and 3 relapses were noted from the 12- and 24-month periods prior to fingolimod onset to the respective periods post-treatment onset ( $p < 0.001$  for both).

**Conclusions:** Fingolimod displays beneficial effects on disability progression, relapse rate and brain MRI outcomes of MS patients in routine clinical practice in Greece. Also, this study supports data of relevant international literature and phase III studies.

## Disclosure

Novartis Hellas S.A.C.I is the sponsor of the study

D.D. Mitsikostas has received grants and honoraria from: Allergan, Amgen, Biogen, Genesis Pharma, Electocore, Eli Lilly, Merck-Serono, Novartis, Roche, Sanofi-Genzyme, Teva. E. Zafeiropoulou is currently a Novartis (Hellas) S.A.C.I employee

I. Iliopoulos received personal compensation from Genesis, Merck Serono, Novartis and Sanofi as member of scientific advisory boards, steering committees or independent data monitoring boards in clinical trials, or as speaker at meetings

N. Fakas has received honoraria from Novartis as a member of scientific advisory boards or, as a speaker in congresses

T. Thomaidis and M. Maltezou have nothing to disclose

N. Grigoriadis received honoraria, travel support, consultancy and lecture fees from Biogen Idec, Novartis, TEVA, Bayer, Merck Serono, Genesis Pharma, Sanofi - Aventis and Research grants from Biogen Idec, Novartis, TEVA, Merck Serono, Genesis Pharma

All authors, except of E.Z are Principal Investigators of the study.



## EP1710

**Biomarkers for monitoring natalizumab treatment in multiple sclerosis**G.H. Bringeland<sup>1,2</sup>, C.A. Vedeler<sup>1,2</sup>, K.M. Myhr<sup>1,2</sup>, S. Gavasso<sup>1,2</sup><sup>1</sup>Department of Clinical Medicine, University of Bergen,<sup>2</sup>Department of Neurology, Haukeland University Hospital, Bergen, Norway

**Background:** Natalizumab is one of the therapeutic monoclonal antibodies developed for prevention of inflammatory attacks in multiple sclerosis (MS). It blocks integrins on leukocytes from adhering to the blood brain barrier, thereby hindering migrating into the central nervous system. All treated patients receive the same dose, but the clinical response is variable and saturation of natalizumab on integrins differs substantially between patients. Natalizumab saturation has been proposed as a biomarker to monitor and patient-tailor treatment, and different methods to measure this on a single-cell level have been proposed in previous flow cytometry studies. We have compared three of these methods, using a new technology for single-cell analysis: mass cytometry by time-of-flight (CyTOF), where antibodies are labelled with metal isotopes instead of fluorochromes, allowing analysis of over 50 parameters in a single cell.

**Methods:** Peripheral blood leukocytes from MS patients receiving natalizumab therapy (n=9) were labelled with antibodies against natalizumab, integrin and cell subtype markers prior to CyTOF analysis. Natalizumab saturation calculated by three previously described methods were compared: 1) natalizumab level compared to a reference sample in vitro saturated with natalizumab, 2) ratio natalizumab/integrin and 3) quantitation of relative numbers of natalizumab and integrin molecules on single cells using beads with known amounts of bound antibodies against natalizumab and integrin as a reference.

**Results:** Numbers of bound natalizumab was positively correlated to numbers of integrin on single cells. After a natalizumab infusion, numbers of both natalizumab and integrin molecules decreased, but the ratio natalizumab/integrin increased. Measuring natalizumab levels alone, therefore gave a false impression of decreasing natalizumab levels after infusion.

**Conclusions:** The method that best reflects saturation of natalizumab on target cells is a combination of previously described techniques: using beads for quantitation of natalizumab and integrin to calculate a ratio natalizumab/integrin. This approach will be of interest for monitoring other therapeutic antibodies.

**Disclosure**

Gerd Haga Bringeland: Nothing to disclose.

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Kjell Morten Myhr: Nothing to disclose.

Sonia Gavasso: Nothing to disclose.

## EP1711

**Long-term experience with natalizumab as first-line treatment for highly active pediatric multiple sclerosis: a case report**

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**Introduction:** Pediatric multiple sclerosis (MS) comprises 2-5% of all cases of MS. Although first-line disease-modifying therapy

(DMT) including interferons appear to be well tolerated in pediatric MS, but recent publications highlight an increasing number of cases resistant to those first-line treatments. There is an urgent need for second-line treatment strategies for pediatric MS, and this is the case of highly active forms.

We report the case of highly active pediatric MS treated with natalizumab as first-line treatment over a period of 36 months.

**Observation:** This is a male child who was diagnosed at the age of 14 with highly active MS and a treatment with NATALIZUMAB 300 mg per month was proposed to him as first intention.

At the initiation of treatment the child's expanded disability status scale (EDSS) was 4, and John Cunningham virus (JCV) serology was negative.

At 6 months of treatment the child had an EDSS of 1 with a persistent MRI activity.

At 12 months, a relapse was reported with an EDSS of 3 and cerebral/medullar MRI revealed a new demyelinating lesions with no signs of activity.

At the 13th infusion, the child's EDSS was 1 and a JCV seroconversion was noted with a JCV index of 0,33. After two years treatment the EDSS was 0 and the JCV index was 0,4 without any MRI activity. The clinical course was performed without any incident and the child had an MRI control and analysis of the JCV index every 6 months up to two years of treatment.

Following a radiological suspicion of progressive multifocal leukoencephalopathy (PML) the treatment was suspended at its 27th infusion and levels of JCV replication in cerebrospinal fluid (CSF) measured via quantitative real-time PCR returned with a negative result. Given the child's good tolerance and its clinical efficacy, the treatment was continued.

Currently the child has received a 36th infusion with a JCV index < 0,9 and no particular incident have been reported up to date. A cerebral MRI control is performed every 3 months with a JCV index analysis every 6 months.

**Conclusion:** Our case report indicate that natalizumab may be safe and effective against highly active MS in pediatric patients. Furthermore, the number of published case studies on children with highly active MS treated with natalizumab also rises, whereas long-term risks as well as therapeutic potential of this therapy in pediatric population have been at the centre of attention.

**Disclosure**

Nothing

## EP1712

**Optimal response to dimethyl fumarate associates in MS with a shift from an inflammatory to a tolerogenic blood cell profile**S. Medina<sup>1</sup>, S. Sainz de la Maza<sup>1</sup>, L. Costa-Frossard<sup>1</sup>, N.Villarrubia<sup>1</sup>, J.C. Alvarez Cermeño<sup>2</sup>, L.M. Villar<sup>1</sup><sup>1</sup>Hospital Universitario Ramon y Cajal, <sup>2</sup>Hospital Universitario Ramon y Cajal, Madrid, Spain

**Background:** The precise mechanism of action of dimethyl fumarate (DMF) treatment in MS remains unknown.

**Objective:** To identify the changes in the blood lymphocyte profile of MS patients predicting no evidence of disease activity (NEDA) status after DMF treatment.

**Methods:** We studied by flow cytometry blood lymphocyte subsets of 64 MS patients treated with DMF at baseline and after six

months of treatment. NEDA (41 patients) or ongoing disease activity (ODA, 23 patients) were monitored after a year of follow-up.

**Results:** During treatment, all patients experienced an increase in the naïve T cells and a decrease in effector memory ones. However, only NEDA patients showed a significant reduction in: central memory CD4<sup>+</sup> and CD8<sup>+</sup> T cells, memory B cells, CD4<sup>+</sup> T cells producing interferon-gamma, CD8<sup>+</sup> T cells producing TNF-alpha and interferon-gamma and B cells producing tumor necrosis factor-alpha (TNF-alpha). Additionally, NEDA patients had an increase in regulatory CD56-bright cells not observed in ODA group. After treatment, there was a negative correlation between CD56-bright cells and CD8<sup>+</sup> T cells producing IFN-gamma and TNF-alpha.

**Conclusion:** A pro-tolerogenic shift in the blood leukocyte profile associates with an optimal response to DMF in MS.

### Disclosure

Silvia Medina, Noelia Villarrubia, and Jose Lifante have nothing to disclose.

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### EP1713

#### Impact of alemtuzumab on work capacity based upon evidence from the CARE-MS II study

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**Background:** MS disease progression negatively affects employment, leading to high economic costs. Hence, therapeutic strategies to reduce disease activity are recommended. In CARE-MS II (NCT00548405), alemtuzumab significantly improved clinical and MRI outcomes vs SC IFNB-1a over 2 years in patients with active RRMS and inadequate response to prior therapy.

**Goal:** To explore potential impact of alemtuzumab on work capacity in CARE-MS II alemtuzumab-treated patients, measured by the Health Resource Utilization questionnaire (HRUQ).

**Methods:** HRUQ evaluates patients' use of healthcare resources, non-medical resources, informal care, and work capacity, and was completed at baseline and every 3 months during the 2-year study by 426 alemtuzumab- and 202 SC IFNB-1a-treated CARE-MS II patients. Questions related to work capacity assessed sick leave due to MS during the past 3 months. Primary analysis excluded sick leave at Months 3 and 15, as it included alemtuzumab treatment at baseline (5 days) and 12 months later (3 days). Statistical analyses to compare alemtuzumab and SC IFNB-1a groups included descriptive analysis, chi-square test on cumulative

percentages over each visit, and generalised linear mixed-effect model for repeated measurements.

**Results:** At baseline, 53.3% and 55.5% of patients randomised to alemtuzumab or SC IFNB-1a, respectively, reported being employed or self-employed. Six SC IFNB-1a and no alemtuzumab patients discontinued study due to lack of efficacy (LOE). During CARE-MS II, the cumulative percentage of alemtuzumab-treated patients taking sick leave due to MS was significantly lower vs SC IFNB-1a-treated patients at Months 6 (11.5% vs 18.8%,  $P=0.018$ ), 9 (15.3% vs 25.9%,  $P=0.002$ ), 18 (24.6% vs 33.5%,  $P=0.023$ ), 21 (26.1% vs 35.1%,  $P=0.022$ ), and 24 (27.7% vs 36.0%,  $P=0.035$ ) and was numerically lower at Month 12 (21.6% vs 27.7%,  $P=0.1$ ). In a longitudinal model over 2 years, alemtuzumab-treated patients took significantly less sick leave due to MS vs the SC IFNB-1a group ( $P=0.04$ ); this finding was confirmed by sensitivity analysis including Months 3 and 15.

**Conclusion:** These exploratory analyses showed that alemtuzumab-treated patients took significantly reduced sick leave due to MS vs SC IFNB-1a over 2 years, a difference that may have been greater if no SC IFNB-1a patients had discontinued due to LOE. These findings suggest that alemtuzumab may offer a unique treatment approach for patients with active RRMS, potentially improving work capacity.

**Study support:** Sanofi and Bayer HealthCare Pharmaceuticals.

### Disclosure

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### EP1714

#### Effectiveness of alemtuzumab in RRMS patients with an EDSS score of $\leq 5$ or $>5$

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**Background:** Alemtuzumab is a disease-modifying therapy (DMT) for the treatment of relapsing-remitting multiple sclerosis (RRMS) that has shown efficacy in reducing the annualized relapse rate (ARR), the risk of sustained disability accumulation, and reduction in gadolinium-enhancing T1 lesions in cerebral magnetic resonance imaging (MRI) in patients with EDSS  $\leq 5$ .

**Objectives:** To study effectiveness outcomes in patients with RRMS with EDSS scores of  $\leq 5$  or  $>5$ .

**Methods:** Retrospective observational study in patients with highly active RRMS treated with alemtuzumab from March 2015 to March 2017 at Virgen Macarena Hospital, Seville, Spain. Demographic/disease characteristics, ARR, changes in disability, and cerebral MRI findings were collected at enrolment.

**Results:** EDSS  $\leq 5$ : 35 patients (23 females), mean age: 36.5 years, mean time to diagnosis 13.2 years. 16 patients have received two cycles of treatment. Mean EDSS score decreased from 3.4 to 2.6 ( $p < 0.05$ ). 22 (62.9%) patients showed a reduction in EDSS, the remaining patients showed no changes in EDSS. ARR decreased from 1.8 to 0.1 ( $p < 0.05$ ). Two patients (5.7%) experienced relapses after two cycles of treatment. T2 lesions on MRI showed no changes, but the mean number of gadolinium enhancing

lesions per patient decreased from 2.7 to 0.2 post-treatment ( $p < 0.05$ ).

EDSS  $> 5$ : 27 patients (18 females), mean age: 42.7 years, mean time to diagnosis: 14.6 years. 14 patients have received two cycles of treatment. Mean EDSS score decreased from 6.6 to 5.9 ( $p < 0.05$ ). 11 (40.7%) patients showed a reduction in EDSS. One patient showed an increase in EDSS of 0.5 points despite receiving the second cycle of treatment. The mean number of T2 lesions on MRI increased from 38.9 to 42.4, and the mean number of gadolinium enhancing lesions decreased from 1.2 to 0.25 ( $p < 0.05$ ).

**Conclusions:** Our data show that alemtuzumab is an effective therapy for the treatment of RRMS irrespective of the EDSS score status, with significant improvement in EDSS score, ARR, and gadolinium-enhancing lesions in patients with EDSS score  $\leq 5$  or  $> 5$ . Larger studies are needed to confirm these results given the relatively small size of our patient population.

### Disclosure

Rocío López Ruiz received honoraria as consultant on scientific advisory boards from Biogen, Novartis and Genzyme.

Sara Eichau received honoraria as consultant on scientific advisory boards from Biogen, Bayer-Schering, Merck-Serono, Teva and Novartis; has participated in clinical trials/other research projects by Biogen, GSK, Teva and Novartis.

JL Ruiz-Peña received honoraria as consultant on scientific advisory boards from Biogen, Bayer-Schering, Merck-Serono, Teva and Novartis; has participated in clinical trials/other research projects by Biogen, GSK, Teva and Novartis.

G. Navarro received honoraria as consultant on scientific advisory boards from Biogen, Bayer-Schering, Merck-Serono, Teva and Novartis; has participated in clinical trials/other research projects by Biogen, GSK, Teva and Novartis.

G. Izquierdo received honoraria as consultant on scientific advisory boards from Biogen, Bayer-Schering, Merck-Serono, Teva and Novartis; has participated in clinical trials/other research projects by Biogen, GSK, Teva and Novartis.

### EP1715

#### Long-term disability outcomes in teriflunomide-treated patients in TEMSO and TOWER: an EDSS and FSS categorical analysis

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**Background:** In both phase 3 clinical trials (TEMSo, NCT00134563; TOWER, NCT00751881) teriflunomide significantly reduced the risk of disability worsening confirmed for  $\geq 12$  weeks in patients with relapsing forms of MS (RMS).

**Objective:** To assess long-term disability outcomes in a pooled analysis of the TEMSo and TOWER core and extension studies.

**Methods:** In TEMSo and TOWER, patients with RMS were randomized 1:1:1 to placebo, teriflunomide

7 mg, or 14 mg. Patients received treatment for 2 years in TEMSo; in TOWER, study duration was variable ending 48 weeks after the last patient was randomized. In the TEMSo extension (NCT00803049), patients randomized to teriflunomide 7 mg or 14 mg continued treatment; those previously receiving placebo were re-randomized 1:1 to teriflunomide 7 mg or 14 mg. All patients received teriflunomide 14 mg in the TOWER extension. Disability worsening was assessed using the Expanded Disability Status Scale (EDSS) and Functional System Scores (FSS). In this pooled analysis of the TEMSo and TOWER core and extension studies (intent-to-treat [ITT] population), EDSS scores were categorized based on change over 1 year, as stable (change from baseline of 0.5 points) or improved (reduction from baseline of 1 point or greater), or worsened (increase from baseline of 1 point or greater); change from baseline at Year 5 is reported for each FSS.

**Results:** The proportion of patients with stable or improved EDSS scores in the overall pooled ITT population remained consistently high over 5 years of treatment with teriflunomide 14 mg (Year 5, 73.6%). This trend was observed in both patients with relapsing-remitting MS (Year 5, 74.0%) and progressive forms of relapsing MS (Year 5, 61.5%). Consistent with these observations of EDSS scores, changes in individual FSS were stable over 5 years (mean [SD] change from baseline at Week 252: Brainstem, 0.05 [0.73]; Bowel & Bladder, 0.12 [0.94]; Cerebellar, 0.20 [0.88]; Cerebral, -0.06 [0.89]; Pyramidal, 0.12 [0.92]; Sensory, 0.18 [1.11]; Visual, 0.01 [0.82]). Disability outcomes were consistent for patients treated with teriflunomide 7 mg.

**Conclusions:** Long-term disability remained stable or improved with teriflunomide in the majority of patients, regardless of MS subtype, which was also reflected in stability across different functional systems. Disability outcomes as measured by FSS were consistent with EDSS outcomes observed in the teriflunomide clinical development programme.

### Disclosure

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**AM:** Consulting fees (Accordant Health Services, Acorda Therapeutics, Alkermes, Biogen Idec, EMD Serono, Genentech/Roche, Genzyme, GSK, Mallinckrodt Pharmaceuticals [Questcor], Novartis, Roche, Teva); contracted research (Biogen Idec, Genentech, Novartis, Questcor, Roche, Sanofi).

**PT:** Employee of Sanofi Genzyme with ownership interests.

**KT and MM:** Employee of Sanofi Genzyme.

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## EP1716

**Long-term efficacy, safety, tolerability and quality of life with fingolimod treatment in patients with multiple sclerosis in real-world settings in France: VIRGILE two-year results**

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**Background:** Fingolimod 0.5 mg daily has an established efficacy, safety and tolerability profile in patients with relapsing-remitting multiple sclerosis (RRMS), with data from a large clinical development programme demonstrating its benefits on relapse rates, disability progression and imaging activity compared to placebo and/or IFNB-1a IM. However, limited data are available in real-world settings, which include patients with a wide range of co-morbidities and concomitant treatments. The French Health Authorities (HAS, CEPS) requested a pharmacoepidemiological study to assess the use and impact of fingolimod in the treatment of highly active forms of RRMS in France. VIRGILE is the largest study in France to date evaluating the long-term efficacy, safety, and tolerability profiles of fingolimod in real-world settings. A natalizumab arm was included in the study.

**Objective:** To assess the effect of fingolimod 0.5 mg on relapse activity, disability progression and quality of life in real-life practice. The study will also describe baseline characteristics of patients treated with fingolimod and natalizumab, and assess the impact of fingolimod treatment on health resource use in both groups.

**Methods:** This is a non-interventional, multicentre, post-authorisation, observational study with prospective follow up of patients treated with fingolimod or natalizumab for 3 years, and potentially an additional 2 years for patients in the fingolimod group. The primary endpoint is the change in annualised relapse rate (ARR) at 2 years compared to baseline (relapse rate in the year prior to treatment). Other endpoints include Expanded Disability Status Scale (EDSS) and tolerability.

**Results:** Enrollment was completed last year, with the inclusion of 1114 patients in the fingolimod arm and 335 patients in the natalizumab arm. Primary outcome results will be presented along with other efficacy and safety results for patients who reached the two-year time point.

**Conclusion:** The results support the long-term efficacy and safety profile of fingolimod in daily clinical practice.

## Disclosure

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GK has received consultancy fees from Biogen, Merck Serono, Novartis, Genzyme, Roche, Teva

MV has received compensation from Novartis for educational activity and consulting

MC disclosures: Biogen, Merck, Novartis, Genzyme

MD has done consulting research and/or workshops for Biogen-Idec, Bayer-Schering, Genzyme, Merck-Serono, Novartis, Sanofi-Aventis and Teva Pharma.

FL and IC are employees of Novartis Pharma S.A.S

## EP1717

**3 year follow-up of 80 patients with RRMS: switching therapies between injectable therapies versus escalation to fingolimod**

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**Introduction:** There is a great controversy in decision making about patients in the early phase of MS, whether to adopt escalation or induction therapy. The existence of multiple injectable therapies (interferons, glatiramer acetate) raises the question to followers of escalation therapy, whether to switch between injectable therapies after relapse or to escalate to higher efficiency drugs, such as fingolimod.

**Method:** We followed 80 patients, 25-35 years old, with RRMS and starting EDSS 0, who after disease relapse EDSS increased to 1. They have been divided in 2 groups of 40 patients each, age and sex matched. The first group was treated with fingolimod 0.5mg, while the second was treated with the same or other form of interferon or glatiramer.

All patients were under clinical follow up every 3 months and MRI imaging every 6 months.

**Result:** Out of the 40 that escalated to higher efficiency, 33 (82.5%) did not present new relapse, and between the rest group 1 patient remained to EDSS 1, 1 ascended to 1.5 and the rest 3 had EDSS 2. From the 33 only 5 (12.5%) presented imaging relapse. The 2<sup>nd</sup> group, showed poorer results, as only 10 (25%) did not present clinical relapse. Among the remaining, 7 had EDSS 1.5, 10 EDSS 2 and 13 EDSS 3.

**Discussion:** It has become evident that the timely switch to higher-efficiency drugs is beneficial to patients, preserving their good clinical and imaging condition, for as long as 3 years after relapse. It seems that timely change of the immunomodulation mechanisms has a positive effect on the disease course. It is very important to note that the spinal cord remains intact for 3 years after escalation.

## Disclosure

Nothing to disclose

## EP1718

**Persistent no evidence of disease activity during natalizumab treatment**

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**Background:** Natalizumab (NAT) is a high effective treatment for relapsing-remitting multiple sclerosis (MS). Pivotal trials and

post-marketing studies showed prolonged disease-free status for patients on treatment.

**Objective:** To evaluate the long-term safety and efficacy of NAT in a monocentric real-world observational study.

**Methods:** We collected data of patients who underwent at least one course of NAT since March 2007 at the MS Centre of San Raffaele Scientific Institute. We analysed clinical and radiological data during NAT therapy. We also reviewed medical charts for side effects.

**Results:** Of the 555 included patients, 69% were female and mean age at inclusion was 33.5 years. Mean disease duration at time of inclusion was 8.6 years, with a mean number of 1.8 relapses in the year before NAT start. Median baseline EDSS was 3.0 and 88% of patients had an active baseline MRI. Mean follow-up on treatment was 3 years (range 1 month–10 years). During NAT treatment annualised relapse rate dropped to 0.26 and only 38% of patients presented at least one active MRI. The probability of disability worsening was 7% at 5 years, while 20% of patients presented a sustained reduction of disability. At 5-year follow-up the overall probability of “No Evidence of Disease Activity (NEDA 3)” was 47%. The most common adverse event was infection (45%) but less than 1% of the patients had to interrupt treatment due to the severity of infection. Seven percent of patients developed anti-NAT antibodies, which were linked to allergic reactions and poor response to treatment. Unfortunately 2 patients developed progressive multifocal leukoencephalopathy.

**Conclusions:** Our data confirm that NAT is to date one of the most effective treatment available and that its benefits are persistent throughout long-term treatment. Our study demonstrated that the drug is well tolerated, improving patients' quality of life. These findings should be carefully pondered, together with information on PML risk stratification, in order to evaluate a personalized benefit-risk profile of NAT.

## Disclosure

Dr. Sangalli, Dr. Radaelli, Dr. Dalla Costa, Dr. F. Esposito have no conflicts of interest relevant to this submission. Dr. Moiola reports speaking fees and/or travel expenses from Merck Serono and from Biogen, outside the submitted work. Dr. Colombo reports speaking fees and/or travel expenses from Merck Serono and from Teva Pharmaceuticals, outside the submitted work. Prof. Comi has received compensation for consulting services and/or speaking activities from Biogen, Novartis, Teva Pharmaceutical Ind, Sanofi, Genzyme, Merck Serono, Biogen, Bayer, Actelion and Serono Symposia Int. Found, outside the submitted work. Dr. Martinelli reports consultancy, speaking fees and/or travel expenses from Biogen-Dompè SG, Merck Serono, Bayer Schering, Novartis, Sanofi-Aventis, Genzyme Europe, Teva Pharmaceuticals, outside the submitted work.

## Risk management for disease modifying treatments

### EP1719

**An investigation into the relationship between the multiple sclerosis Impact Scale (MSIS-29) and Predicted Medication Adherence as measured by the Morisky Medication Adherence Scale (MMAS-8)**

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**Objective:** To examine the specific relationships between global and subscale scores of the MSIS-29 and MMAS-8 in people with Multiple Sclerosis (PwMS).

**Background:** (PwMS) have multiple treatment choices for disease modifying therapies (DMT). DMT non-adherence and treatment delay impacts outcomes and costs. Adherence can be measured by patient report, observation and refills. With varied DMT choices, routes and frequency, predicted PwMS adherence behavior needs exploration as this might impact choice. Non-adherence factors (purposeful vs. accidental) remains unexplored in PwMS. MMAS-8, a validated 8 point questionnaire, is predictive of: medication adherence, pharmacy fill data, and efficacy, economic outcomes, and can be graded to analyze purposeful and accidental sub-scores of non-adherence. This information, when paired with disability measures, might improve both understanding and addressing PwMS non-adherence, and perhaps resultant related disease progression.

**Methods:** Retrospective reviews of PwMS who completed MSIS-29 and MMAS-8 on the same day in the course of routine clinical care. Global scores for each scale, MSIS-29 physical and cognitive subscales, and MMAS-8 purposeful and accidental subscales were included. Multivariate regression analysis was used to analyze the relationships between scales. Significance was set at  $p < 0.01$ .

**Results:** 245 PwMS; average age=49.8±10.8, 73.5% female. Significant relationships were as follows: MSIS-29 global with MMAS-8 global ( $r=0.19$ ,  $p < 0.01$ ) and accidental ( $r=0.22$ ,  $p < 0.001$ ); MSIS-29 physical with MMAS-8 accidental ( $r=0.17$ ,  $p < 0.01$ ), and MSIS-29 cognitive with MMAS-8 global ( $r=0.24$ ,  $p < 0.001$ ), purposeful ( $r=0.18$ ,  $p < 0.01$ ), and accidental ( $r=0.28$ ,  $p < 0.00001$ ).

**Conclusions:** Factors in non-adherence in MS is complex and the most consistent relationships was between accidental non-adherence and self-reported cognitive impairment. Providers should consider therapies that are not self-administered when prescribing DMT to cognitively impaired PwMS.

## Disclosure

All authors: nothing to disclose

### EP1720

**TRUST - evaluation of baseline data to investigate an integrated approach for optimised patient management in multiple sclerosis patients treated with natalizumab**

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**Background:** In order to improve treatment decisions in natalizumab-treated relapsing-remitting multiple sclerosis (RRMS) patients at higher risk for progressive multifocal leukoencephalopathy (PML), standardised monitoring procedures may provide a superior basis for individual benefit/risk evaluation. However, management of these patients in the clinical practice in Germany is highly heterogeneous.

**Goals:** Key goals of the prospective, non-interventional TRUST study are to assess the course of disease over 36 months in patients with sustained natalizumab therapy versus those who discontinue natalizumab treatment and to evaluate the use and effects of an integrated, adaptive patient management approach.

**Methods:** The ongoing TRUST study enrolls up to 1260 RRMS patients treated with natalizumab for  $\geq 12$  months. Patients are documented over 3 years irrespective of treatment changes. Endpoints include clinical, subclinical, and patient reported outcomes as well as utilisation of risk-stratification tools and expert advice in the clinical routine. This interim analysis presents baseline data at the end of the recruitment period (cut-off date Jan 17, 2017).

**Results:** The full analysis set of this interim analysis comprised 1186 patients (71.8% female, mean [ $\pm$ standard deviation, SD] age 39.2 $\pm$ 10.1 years) from 154 sites. Mean ( $\pm$ SD) EDSS score at start of natalizumab was 3.1 $\pm$ 1.6. The pre-study annualised relapse rate (ARR) before and after starting natalizumab was 2.09 and 0.15, respectively. Patients received 43.0 $\pm$ 29.7 (mean $\pm$ SD) natalizumab infusions before study inclusion. At baseline, 95.5% of patients had John-Cunningham-virus (JCV) antibody tests and 96.9% of patients had initial magnetic resonance imaging data available. Until April 20, 2017, 20 cases of suspected PML were reported (8 were confirmed and 12 were ruled out) and expert opinion was requested by 13 sites (46 requests in total), mostly focusing on PML risk assessment. 9.4% of patients discontinued natalizumab after study inclusion.

**Conclusion:** The TRUST study examines a population of MS patients with high disease activity as seen by their ARR before natalizumab start. Compared to the first interim analysis (n=427), there were slight increases in the number of patients with available JCV antibody tests. As follow-up continues irrespective of natalizumab discontinuation, TRUST will provide insight into individual benefit/risk considerations and decision making in clinical routine practice.

## Disclosure

The TRUST study is funded by Biogen GmbH, Ismaning, Germany.

Hans-Peter Hartung has received fees for consulting, speaking and serving on steering committees from Bayer Healthcare, Biogen Idec, CSL Behring, GeNeuro, Genzyme, MedImmune, Merck Serono, Novartis, Opexa, Receptos, Roche, Sanofi and Teva, with approval by the Rector of Heinrich-Heine-University.

Jens Wuerfel is CEO of MIAC AG. He served on advisory boards for Actelion, Biogen, Genzyme, Novartis, Teva, TG Therapeutics and Roche. He received speaker honoraria from Bayer, Biogen, Genzyme, Novartis, and Teva, and expert reading compensation from mediri. JW was supported by the DFG, the EU, the German ministry of education and research (BMBF/KKNMS) and the German ministry of economy (BMWi).

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## EP1721

### severe rebound tumefactive relapse in a MS patient on Lemtrada

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**Case history:** A 19 year old Asian patient with known relapsing remitting multiple sclerosis (MS), presented with a very severe multifocal rebound relapse 10 months after his first Lemtrada



infusion. He initially presented in September 2014 with left-sided weakness, paraesthesia and ataxia and was started on Avonex. He was switched to Lemtrada in July 2015 following a brain stem relapse and radiological progression. His lymphocyte recovery started within 2 weeks and his lymphocyte levels 6 months post Lemtrada were near normal. In mid-April 2016 he presented with slurred speech and drooping on the right side of his mouth. On 4<sup>th</sup> May 2016 he was admitted to hospital with progressive dysarthria, diplopia, unsteadiness, left sided facial and lower leg numbness. He was given high dose intravenous methylprednisolone but continued to deteriorate requiring intubation and ventilatory support. Serial MRIs showed active tumefactive MS with almost entire brainstem involvement as well as large hemispheric tumefactive lesions. He was given a further course of steroids, plasmapheresis and six doses of cyclophosphamide. Following this he stabilised radiologically and clinically and was eventually moved back to the ward. In August 2016 he was discharged to a rehabilitation hospital. Seven months following discharge he was reviewed in MS clinic and has shown remarkable recovery with a jerky smooth pursuit and inability to perform tandem gait. His EDSS is 2. His MRI of the brain showed almost complete resolution of the previously seen lesions.

**Discussion and conclusion:** Lemtrada is a humanized monoclonal anti-CD52 antibody that causes rapid and prolonged pan-lymphocyte depletion with relatively rapid and disproportionate B-cell repopulation. Our patient showed rapid lymphocyte reconstitution starting within 2 weeks of his Lemtrada infusion which potentially played a role. As suggested by Gold and colleagues this rare rebound inflammatory phenomenon could be B-cell driven. Cyclophosphamide effect on T cells is to induce apoptosis and rapid cell death as well as to suppress antibody production. Our patient made a remarkable clinical and radiological recovery with relatively little neurological sequelae. Cyclophosphamide should be considered as a rescue therapy in cases of rapidly progressive rebound inflammatory disease post-Lemtrada. The role of B-cells in rebound disease post-Lemtrada should be explored further.

### Disclosure

Dr. Sonia Kumari: nothing to disclose

Dr. Gordon Mazibrada: has served at advisory boards for Biogen, Merck, Teva, Novartis, Genzyme and Roche and our MS department has received funding from those companies for research projects and service developments.

### EP1722

#### Secondary antibody deficiency and infection following B-cell depletion for CNS neuroinflammation

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B-cell depleting anti-CD20 monoclonal antibody therapies have demonstrated promising clinical efficacy in suppressing relapses in individuals with neuromyelitis optica (NMO) and multiple sclerosis (MS). However, uncertainties remain about the optimum treatment schedule. In rheumatological disease, anti-CD20 agents are most often employed for short-term induction therapy and are subsequently replaced by longer-term maintenance therapy. In contrast, repeated cycles of anti-CD20 monoclonal

antibody therapy are proposed as maintenance therapy for CNS neuro-inflammatory disorders. Post-marketing surveillance will be essential to fully uncover the long-term safety profile of repeated B-cell depletion. Hypogammaglobulinaemia is a recognised consequence in a proportion of patients treated with medium- to long-term B-cell therapy and may play a role in the increased incidence of infection observed in the anti-CD20 arms of treatment trials. We report 5 cases of serious infection associated with hypogammaglobulinaemia occurring in patients receiving rituximab for NMO. The cases were all female, all had low IgG with variable reductions in IgM and IgA. The cases had a mean treatment duration of 3.1 years, but not all cases had had extensive exposure (treatment duration range 0.5 - 6.2y). We review the evidence relating to hypogammaglobulinaemia following anti-CD20 treatment for neuroinflammatory disorders and propose an algorithm for monitoring and treatment of this recognised complication.

### Disclosure

E C Tallantyre: has received research support from Biogen Idec.

D Whittam: nothing to disclose.

N P Robertson: has served on the scientific advisory board for Genzyme, Roche, Novartis, and Biogen, received travel funding and/or speaker honoraria from Biogen and Genzyme and received research support from Genzyme, Novartis, National Institute of Health Wales, Multiple Sclerosis Society of Great Britain, and Northern Ireland Wellcome Trust.

A Jacob: has received research grants from Biogen Idec, Alexion Pharmaceuticals and speakers fees from Biogen, Chugai, Sanofi-Genzyme and Terumo-BCT.

### EP1723

#### Progressive multifocal leucoencephalopathy in patient with fingolimod treatment: one-year follow-up

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Awareness of Progressive multifocal leucoencephalopathy (PML) has increased in recent years, with the description of cases related to disease modifying therapy in multiple sclerosis (MS).

We present a case of PML affecting a patient with MS treated with fingolimod.

A 60 year-old female patient affected by MS since 1993, presented in June 2016 subacute onset of apraxia. She took fingolimod uneventfully since March 2012. She had previously received treatment with interferon Beta 1a for 3 years. Previous medical history was negative. Routine white blood cell count showed a lymphocytopenia with a variable value from 700/mm<sup>3</sup> and 300/mm<sup>3</sup>.

In May 2016 pts presented a minimal worsening of paraparesis with more fatigue and slowness. We plan a strict clinical-radiological follow-up. One month later patient presented inability to control movement. Brain MRI revealed multifocal non enhancing white matter (WM) T2 hyperintensity, involves subcortical U-fibers in frontal and parieto-occipital areas. Cerebrospinal JCV viral load was 1000 copies/ml. White blood cell count showed a leucocytopenia (3600/mm<sup>3</sup>) and lymphocytopenia (400/mm<sup>3</sup>). Stratify JCV was positive (3,82). We immediately stopped treatment; other immunocompromise causes were excluded.

Neuropsychological tests revealed cognitive impairment focused on attentional systems and ideomotor/ideational apraxia. We planned monthly MRI in order to identify immune reconstitution inflammatory syndrome. Clinical progress was insidious and reached the nadir in september when patient presented constructional/spatial defects, dressing apraxia, dysgraphia, dyscalculia and worsening of motor weakness. Serial MRI showed progression of the patchy WM lesions without enhancement; increased signal intensity on T2-weighted and diffusion-weighted images suggested an active inflammatory process. We never prescribed steroids. Four month after drug discontinuation cerebrospinal JCV viral load was negative.

Since october 2016 clinical status slowly improved and MRI showed stabilized lesions. Patient underwent to rehabilitation: now she required unilateral assistance to walk and retains most self-care functions.

Actually 9 cases of PML are reported in MS patients on Fingolimod treatment; all patients are over 50 years old, suggesting immunosenescence as main promoting factor. No one has been fatal. MRI and neuropsychological assessment are precious tools to recognize PML in subclinical phase in order to optimize the management of disease.

## Disclosure

Francesca Rossi: nothing to disclose

## EP1724

### **Incidence of cervical dysplasia in females receiving alemtuzumab: an Australian single centre observational study** C. Nesbitt, L. Rath, O. Skibina

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**Background:** Cervical Dysplasia (CD) is linked to the Human Papilloma Virus (HPV). Immunocompromised patients are therefore thought to have an increased risk of CD, and to develop dysplastic changes faster compared to immunocompetent individuals. CD screening is recommended with Alemtuzumab, however there is no data regarding the incidence of CD in Multiple Sclerosis (MS) patients exposed to this treatment.

**Goal:** To ascertain the incidence of CD in patients receiving Alemtuzumab. Our secondary goal was to assess the role for HPV dna testing in determining patient risk.

**Methods:** We collected data from all 11 female patients treated with Alemtuzumab at the Alfred from 2014 to present. All patients had a pap test prior to treatment, and 3 out of 11 self funded additional HPV dna testing. Patients with abnormal pap tests or positive high risk HPV dna were referred to gynaecology for ongoing 6 monthly follow up. Patients with normal pre-treatment tests were advised to have ongoing annual testing. All abnormal pap tests were confirmed with colposcopy.

**Results:** Data was collected over a crude period of 13.25 patient years. 2 patients with normal initial pap tests developed changes (1 with low grade squamous epithelial lesion LSIL, and 1 with high grade squamous epithelial lesion HSIL). These changes were identified at a 6 month follow up interval. Both patients who developed CD changes tested positive for high risk HPV dna.

The crude incidence of HSIL in our Alemtuzumab treated patients with an additional positive high risk HPV tests was 55.5 per 100

patient-years. The population incidence of HSIL with a positive high risk HPV test is 0.25 per 100 patient-years suggesting a significant increased risk for patients who are exposed to Alemtuzumab.

**Conclusion:** This sample is too small to have meaningful statistical significant but does support concerns that exposure to immunosuppressing therapies including Alemtuzumab increases risk of CD.

MS patients are typically young and female who will have long term exposure to immunosuppressants. We recommend CD screening become a part of routine clinical care and to consider closer surveillance than the usual population screening protocols.

All patients in this study who tested positive for high risk HPV dna prior to Alemtuzumab treatment developed dysplastic changes on follow up testing. We advocate for additional HPV dna testing to be performed to help identify patients who warrant closer surveillance.

## Disclosure

Dr Skibina and Dr Nesbitt have both previously received sponsorship from Genzyme to attend educational meetings. There was no funding provided for this research project.

Louise Rath has no significant disclosures

## EP1725

### **Myocardial ischemia associated with alemtuzumab infusion in multiple sclerosis: a case report**

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<sup>2</sup>Cardiology, Civil Hospital, Azienda Ospedaliero-Universitaria, Modena, Italy

**Introduction:** Alemtuzumab is an anti-CD52 monoclonal antibody widely used for the treatment of relapsing-remitting multiple sclerosis (RRMS) with high disease activity despite previous disease-modifying therapies.<sup>1</sup> The most common infusion-associated reaction (IAR) is cytokine-release syndrome. Incidence of cardiac-related IARs is 12.5% (tachycardia, bradycardia, palpitations), of which only 0.5% are serious cardiac-related IARs such as atrial fibrillation, sinus bradycardia, sinus tachycardia, hypotension or hypertension.<sup>2</sup>

We report a serious cardiac-related adverse event occurring during alemtuzumab-infusion in a RRMS patient.

**Case report:** A female 24-year-old RRMS patient, with an unremarkable personal history, started treatment with alemtuzumab due to ongoing disease activity during treatment with natalizumab. On the third day of treatment, shortly after premedication with steroids, antihistamine drugs, paracetamol and lansoprazole, the patient developed severe asymptomatic sinus bradycardia, which was treated with intravenous atropine. Infusion of alemtuzumab was resumed but on the following morning she complained of oppressive chest-pain lasting 20 minutes associated with dyspnoea. Blood tests showed high levels of troponin I, creatine kinase MB, and D-Dimer. Alemtuzumab treatment was discontinued. Continuous cardiac monitoring showed mild bradycardia in the absence of cardiac arrhythmias. Electrocardiography revealed a prolonged QTc interval. Echocardiography and cardiac magnetic resonance imaging did not detect alterations of left ventricular function nor the presence of regional wall-motion abnormalities.

Computed tomography angiography and doppler ultrasonography of lower limbs did not reveal signs of acute pulmonary embolism/deep venous thrombosis. Within the subsequent week, myocardial cytolysis enzymes and D-dimer spontaneously returned within normal ranges and QTc interval normalized.

**Conclusion:** To our knowledge, this is the first report on a possible association between alemtuzumab treatment and acute coronary syndrome in absence of cardiovascular risk factors. We speculate that the augmentation of endothelial and myocyte membrane permeability and vasodilation induced by alemtuzumab-related cytokine-release syndrome might determine supply/demand ischemia of myocardic muscle defining type 2 myocardial ischemia.<sup>3</sup>

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Patrizia Sola: nothing to disclose

### EP1726

#### Evaluation of the benefit of an initial risk-assessment and individualized patient coaching for adherence for three different-modifying therapies

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<sup>1</sup>Konzept Pharma Service GmbH, Elze, <sup>2</sup>Biogen GmbH, Ismaning, <sup>3</sup>Juliusspital, Würzburg, Germany

**Background:** Patient support programs (PSPs) contribute to the adherence to prescribed multiple sclerosis (MS) therapies. Beside therapy-dependent side effects, conscious and unconscious factors as well as personal circumstances are crucial for therapy adherence. By considering these aspects, PSPs for three disease-modifying therapies (DMTs) were established. The aim of this analysis is to evaluate the benefit of patient classification by risk factors to favour adherence through an individualized coaching.

**Methods:** From February 2014 dimethyl fumarate (DMF), September 2014 peginterferon beta-1a (PEG) and August 2016 daclizumab beta (DAC BETA) patients were recruited and signed a written consent form. Each PSP considers potential adherence barriers for instance prior therapies and personal circumstances. At therapy start patients were stratified into subgroups displaying high, medium and low risk for non-adherence. Contents and frequency were adapted according to expected challenges and patient needs.

**Results:** As of April 2017, 16480 patients taking any of the three DMTs were recruited. 4871, 2842 and 117 patients were stratified for DMF, PEG and DAC BETA, respectively, according to individual adherence risks. DMF patients were stratified at therapy start into high (24.2%), medium (34.4%) and low (41.0%) adherence subgroups. PEG patients were categorized by cumulative adherence risks into five subgroups from 1 for high up to 5 for low adherence (14.2%, 42.4%, 40.8%, 2.2%, 0.4%). Non-adherence was measured by therapy discontinuation and analyzed. For DMF and PEG dropout rates correlated with assessed adherence risks. After

one year DMF therapy discontinuation was 16.5%, 20.9% and 24.7% for high, medium and low adherence subtypes, respectively. PEG subgroups also demonstrated more susceptibility for therapy discontinuation depending on the present adherence risks. One year dropout rates were 15.2%, 19.9%, 23.6%, 43.8% and 45.5% for patient subtypes 1, 2, 3, 4 and 5. For DMF, adherence subtypes were re-classified after 1 year of appropriate coaching displaying a shift of the number of patients from low to the high adherence subtype.

**Conclusion:** Present data demonstrate that patient stratification based on identified risk factors can predict non-adherence. In turn, subtyping of patients can be useful to provide an adjusted support according to patient needs. Risk-adopted, individualized coaching is suitable to reduce adherence barriers and to promote adherence.

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**YBN:** received funding for medical writing.  
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### EP1727

#### The results of a controlled, prospective study of relapsing MS patients at risk for PML who switched from long term natalizumab to teriflunomide in a controlled, prospective study

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**Background:** Natalizumab (NTZ) has the risk of causing progressive multifocal leukoencephalopathy (PML) in patients after extended use and with detectable anti-JCV-antibodies. There is a need for alternative disease modifying treatment (DMT) that would be safe and effective to prevent recurrence of MS exacerbations upon discontinuation of NTZ without further risk of PML. Platform DMTs have been ineffective in preventing rebound of MS activity. Fingolimod and dimethyl-fumarate (DMF) have associated with PML. No cases of PML have been associated with teriflunomide in 70,000 patients.

**Objectives:** To explore the safety and efficacy of teriflunomide in patients switching from NTZ to teriflunomide in MS patients at risk for PML.

**Methods:** Patients with relapsing multiple sclerosis (RMS) must have received 12 or more NTZ treatments and be anti-JCV-ab positive and not have had prior immunosuppressive therapy. Patients had to be free of clinical relapses during prior 12 months of NTZ treatment. RMS patients ages 21 to 65 began teriflunomide at 14mg daily, within 4 weeks after last dose of NTZ. Relapse assessment, EDSS, 3T brain MRI, laboratory tests were performed at baseline and monthly for 6 months. Final assessments were done at 12 months.

**Results:** There were 62 patients screened and 55 enrolled. Mean age was 47 (SD 10.16). Seventy six percent were female. The mean EDSS at baseline was 3.03 (SD 1.35); 47 patients completed 12 months with mean EDSS of 2.98 (SD 1.44). The mean number



of NTZ treatments prior to treatment with teriflunomide was 43 (SD 25.86).

MRI results showed 38 patients (69%) stable in all parameters from baseline to month 12. Seventeen patients had a new MRI lesion during the 12 months. There were 12 patients with Gd+ enhancing lesions, 13 patients with new T2 hyperintensities and 5 patients with enlarging lesions. Most of the patients with new MRI lesions had no symptoms. Only three patients required change of DMT due to MRI progression. Seven patients dropped out of the study due to adverse events or lack of efficacy.

**Discussion:** These results show that, in the majority of patients, teriflunomide may be a rational choice for long term safety and efficacy for patients at risk for PML. Early switch, in fewer than 4 weeks, from NTZ to teriflunomide, may be important to suppress ongoing 'rebound' and recurrent MS activity after stopping NTZ.

### Disclosure

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SC: Serves on steering committees and advisory boards for Biogen, Novartis, Sanofi-Genzyme and Mallinckrodt, receives research support from Biogen, Novartis, Sanofi-Genzyme, Roche, Opexa, and Mallinckrodt, receives speaking honoraria from Biogen, Novartis, Sanofi-Genzyme and Acorda;

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### EP1728

#### Hepatic toxicity appears infrequently and early after initiation of teriflunomide in real-world practice: a multicenter, 2 years follow-up retrospective study

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**Introduction:** Teriflunomide (TER) has been subjected to a special monitoring for hepatic toxicity, as it could be observed in multiple sclerosis (MS) clinical trials (CTs), but it is necessary to investigate what happens in real-world practice, where TER has been used mainly after first-line disease-modifying drugs (DMD)

**Objective:** To analyze safety and tolerability of TER.

**Methods:** We retrospectively recorded clinical and biochemical data from MS patients who underwent teriflunomide from 6 Spanish hospitals.

**Results:** A total of 255 records from MS patients (mean of age = 45.27 ± 11.5 y; 184 females) who initiated TER (mean on-treatment time = 13.1 ± 6.7 mo) from december 2014 to march 2017, were reviewed. Regarding the MS type, most of them (n = 242; 174

females) were classified as relapsing-remitting form, and 13 as progressive active forms (12 SP, 1 PP). Mean disease duration was 10.92 ± 8.5 y; range = 0-37 y). A total of 171 patients had been previously on at least one DMF (43.13% from IF, 8.23% from GA, 2.74% from NTZ, 3.13% from FTY, and 7.45% from DMF), 37 patients switched to TER because of inefficacy, and 134 patients for intolerance or side effects. A 40.8% of patients on TER experienced some adverse events (AE). Most common AEs were abdominal complaints (23.5%), hair thinning or decreased hair density (16.9%). AEs, leading to discontinuation appeared in 15 patients (6%), mainly diarrhea (n = 4; 26.7%). Serious adverse events accounted for 13 patients, included 5 patients with stomatitis (1 herpetic), 1 case with lymphopenia (< 900 cel/mm<sup>3</sup>), and pregnancy in 2 females. Hepatic toxicity was temporarily observed in 22.7%, being less than 3x normal range in 48.5% of them, and in only one case exceeded x3 normal range. First ALT increase was recorded during the first 3 months for 91.9% of patients.

**Conclusions:** In real word practice, teriflunomide was generally well tolerated. Hepatic toxicity was mild and temporarily found in the first 3 months, leading to discontinuation for only one patient (0.4%). These results do not justify the number of blood draws needed for monitoring teriflunomide potential hepatic toxicity.

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Oliva P has received honoraria from Biogen Inc., TEVA, Novartis, Merck, Sanofi Genzyme, Roche.

Ares A has received honoraria for speaking or advisor from Biogen Inc., TEVA, Novartis, Merck, Sanofi Genzyme.

Hernandez L has received for speaking or advisor honoraria from Biogen Inc., TEVA, Novartis, Sanofi Genzyme.

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Solar DM has received honoraria for speaking or advisor from Biogen Inc., TEVA, Novartis, Merck, Sanofi Genzyme, Bayer, and Roche.

Suarez R has received honoraria for speaking or advisor from Biogen Inc., TEVA, Novartis, Merck, Sanofi Genzyme.

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### EP1729

#### Mortality from *Listeria monocytogenes* meningoencephalitis following escalation to Alemtuzumab therapy for relapsing-remitting multiple sclerosis

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A 42 year old Caucasian female died from Listeriosis a week following Alemtuzumab administration, one month after discontinuing dimethyl fumarate.

This is the first mortality of a complication to which patients appear particularly vulnerable days/weeks post-administration.

Multiple Sclerosis was diagnosed in 2014. Relapse in March 2015 lead to dimethyl fumarate initiation in July 2015.

Further relapses arose in August 2015 and April 2016. Dimethyl Fumarate was discontinued in July 2016. Expanded Disability Severity Scale score was 2.5. In August 2016 Alemtuzumab 12mg iv was administered for five days with 1gram Methylprednisolone for the initial 3 days.

At day 6 post-completion, a 3 day history of diarrhoea, vomiting and malaise was reported and rapid deterioration supervened. Paramedics found the patient comatose (GCS 7; E4, V2, M1) with severe tachypnoea (60 breaths/minute), high-grade pyrexia of 40C, tachycardic and hypertensive. She was intubated on scene.

CT head revealed reduced grey-white differentiation, diffuse cerebral swelling, bilateral temporal horn distension and cisternal effacement consistent with severe meningoencephalitis. Laboratory studies demonstrated a grossly elevated C reactive protein in the absence of a peripheral leucocytosis.

Eight hours after admission her pupils became asymmetrically fixed. External ventricular drainage decompressed intracranial pressure >30cmCSF; the fluid was clear and colourless, yielding only 5 white cells and 279 red cells, protein .33g/l and a raised glucose gradient of 2.8mmol/l in CSF vs. 8.1mmol/l in serum.

Therapy included Ceftriaxone 2g b.d., Aciclovir 700mg t.d.s. and Amoxicillin 2g four hourly.

CSF PCR yielded a positive result for *Listeria monocytogenes*. Despite resolution of pyrexia and improving inflammatory indices a diagnosis of brain death was recorded at 60 hours following admission. Cultures of blood and CSF later supported the diagnosis of listeriosis.

There was considerable overlap with typical post-infusion symptoms therefore high surveillance and low threshold for empirical or possible prophylactic co-trimoxazole therapy is advocated.

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## EP1730

### Clinical activity after fingolimod cessation: disease reactivation or rebound?

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**Background:** In the last years several reports about a possible rebound after fingolimod discontinuation in patients with Multiple Sclerosis (MS) were reported. On the other side, no rebound was found in the fingolimod randomized clinical trials, including more than 2000 subjects. It is still debated if the so-called rebound is really related to fingolimod discontinuation rather than the natural course of highly active MS.

**Objective:** The study aimed to survey the prevalence of severe reactivation and rebound after fingolimod discontinuation in a large cohort of MS Italian patients.

**Methods:** Patients with RRMS treated with fingolimod since at least 6 months, who stopped treatment for reasons not related to inefficacy were included in this analysis. A severe reactivation was defined as a relapse with an associated EDSS increase of at least 2 points or 2 or more relapses in the 6 months following fingolimod discontinuation. A severe reactivation was considered a rebound if these criteria have never been fulfilled in the patient's previous medical history.

**Results:** A total of 108 patients (mean age: 37.3 (SD:10); females: 79.6%; median EDSS: 2.5 (0-8.5); disease duration: 10.6 years) satisfied the inclusion criteria; we selected 90 patients with no relapses in the last 6 months under fingolimod. 13 out of 90 (14.4%) patients had a relapse within 3 months after fingolimod discontinuation (9 without any new therapy), and further 10 (11.1%) had a relapse within 6 months (6 without any new therapy). Six out of 90 (6.5%) patients had a severe reactivation. Among them, 1 had a relapse associated with an EDSS increase of 6 points, 2 had a relapse associated with an EDSS increase of 2 points and 1 had 3 relapses over 6 months. Four patients out of 90 (4.4%) were defined as rebound.

**Conclusions:** The present study showed that more than 25% of patients risk to have a relapse within 6 months after fingolimod discontinuation. This is an expected result, being fingolimod approved in Italy as second line therapy in MS. Nevertheless, the risk of severe reactivations and rebound is lower than previously described.

## Reference

Hatcher SE, et al. Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment

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G Fenu received consulting fees from Biogen Idec, Merck Serono, Teva, Genzyme, Novartis.

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D Baroncini received speaking honoraria and fees for advisory board, travel and editorial projects from Almirall, Sanofi-Genzyme, Merck, Novartis, Teva

P Annovazzi received speaking honoraria and/or fees for participating to advisory boards and/or travel expenses for participating to congresses and meetings from Teva, Biogen, Novartis, Roche, Almirall, Sanofi Genzyme and Merck

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## EP1731

### Delayed lymphocyte re-population following discontinuation of dimethyl fumarate and after switching to other disease modifying drug therapies

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**Background:** Dimethyl fumarate (DMF) reduces absolute lymphocyte counts, CD4, and CD8 counts, without significantly affecting total white blood cell counts. However, the recovery rate of these cells after discontinuation of DMF is unknown. The effect of subsequent disease modifying therapies (DMTs) on re-population rate is also unknown.

**Objectives:** First, to study the re-population rate of absolute lymphocytes, CD4, and CD8 counts back to baseline after discontinuation of DMF. Second, to measure the effect of subsequent DMTs on the re-population rate of these cells after DMF therapy. Third, to study the effect of the duration of exposure to DMF on repopulation of these cells.

**Methods:** A retrospective chart review of subjects who had discontinued DMF and in whom, CBC with differential, CD4 and CD8 counts were available at baseline, discontinuation and follow-up (n=113). Linear mixed models were used to analyze and assess linear trends in lymphocyte counts after DMF had been discontinued.

**Results:** DMF causes a significant drop in absolute lymphocyte, CD4, and CD8 counts. Re-population of these cells after discontinuation of DMF is significantly delayed, irrespective of whether or not a subsequent DMT is used, although there is a difference in re-population rate among DMTs. Repopulation rate was the

shortest for glatiramer acetate (or on no therapy); no recovery was observed with fingolimod or with alemtuzumab at the conclusion of our study. The re-population rate is also dependent on the duration of time patients have been exposed to DMF; longer exposure was associated with more delayed recovery. One extra month on DMF was significantly associated with a 4% decrease in the monthly rate of change for CD4 counts, 6% decrease in the monthly rate of change for CD8 counts and a 3% decrease in the monthly rate of change for the absolute lymphocyte count.

**Conclusion:** During this 30 month study period, re-population rates were significantly delayed post-DMF. Furthermore, no recovery of lymphocyte counts occurred in patients who were started on fingolimod or alemtuzumab after DMF was discontinued; in fact there was a continued decline in all of the cell populations studied.

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Tayo Olapo: Nothing to disclose

## EP1732

### Teriflunomide (Aubagio®) International Pregnancy Registry: enrolment update

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**Background:** Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS in 70 countries, with more than 71,000 patients currently being treated with teriflunomide worldwide. Teriflunomide is contraindicated in pregnancy based on embryo-foetal toxicity in rats and rabbits. Despite the requirement to use effective contraception during teriflunomide clinical trials, pregnancies did occur. There were no signs of structural or functional deficits in newborns and data from the clinical programme, although limited due to the low number of pregnancies, showed no signal for human teratogenicity. It is, therefore, important to continue to collect data on teriflunomide exposure in pregnancy.

**Objective(s):** The International Teriflunomide Pregnancy Exposure Registry will compare rates of birth defects (congenital malformations, foetal deaths, termination due to foetal abnormality) in teriflunomide-exposed pregnant women with those reported by the European Surveillance of Congenital Anomalies (EUROCAT).

**Methods:** The registry is a voluntary, multinational, prospective, observational, exposure-registration study. Pregnant women with MS with teriflunomide exposure (any dose, any time after Day 1 of last menstrual period until pregnancy end) can enrol. National Coordinators will liaise with healthcare professionals to collect information on teriflunomide-exposed pregnancies and coordinate patient enrolment in the registry. Target recruitment is 196



women to achieve 104 live births, providing an 80% power to detect a 3.95-fold increase in risk ratio of birth defects associated with teriflunomide exposure vs EUROCAT. Pregnancy outcome data including birth defects and infant characteristics during the first year of life will be collected.

**Results:** As of April 26, 2017, 14 patients have been recruited from 7 countries in Europe. Six healthy babies have been born with no abnormality reported to date. One patient had an elective termination that was not motivated by either an abnormal result of a prenatal test or by any concerns regarding potential birth defect.

**Conclusions:** This registry aims to provide data on pregnancy outcomes and infant development during the first year of life from teriflunomide-exposed pregnancies and will help physicians to provide better counselling for women exposed to teriflunomide during pregnancy.

### Disclosure

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**PT:** Employee of Sanofi Genzyme, with ownership interest.

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### EP1733

#### Unexpectedly high rate of discontinuation of pegylated interferon beta-1a among previously stable interferon-treated patients due to poor tolerability and disease recurrence

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**Background:** Biweekly pegylated interferon beta-1a (PEG-IFN, Plegriby) is an attractive treatment option for multiple sclerosis (MS) patients currently treated with interferons. However, the efficacy and tolerability of PEG-IFN treatment in this population is unknown, as only 1% of the patients in the pivotal trial of PEG-IFN were previously treated with interferons, and a subsequent interferon-to-PEG-IFN switch study focused primarily on flu-like symptoms and their management.

**Objective:** To evaluate the efficacy, tolerability and 12-month discontinuation rates of PEG-IFN among MS patients previously stable on another interferon.

**Methods:** In this retrospective two-centre study, we reviewed the medical records of 116 MS patients who initiated treatment with PEG-IFN between November 2014 and March 2016. We limited the analysis to 73 patients who were previously treated with interferons with no evidence of disease activity (as determined by the absence of relapses and/or MRI lesions) prior to initiation of PEG-IFN. The primary outcome was the rate of PEG-IFN discontinuation in the first 12 months. Secondary

outcomes were the reasons for PEG-IFN discontinuation and evaluation of MS activity (relapse or new MRI lesions) during the initial

12 months of PEG-IFN treatment. Chi-square and t-test were used to assess differences between categorical and continuous variables, respectively.

**Results:** The study population consisted of 73 patients (85% female) previously treated with interferon for 7.4 $\pm$ 4.7 years, with no evidence of relapses or MRI changes for median 18 months (range 6-58 months from last MRI prior to PEG-IFN initiation). Within the first 12 months of switching to PEG-IFN, 29 (40%) discontinued PEG-IFN, due to poor tolerability (n=19, 26%) and MS relapses (n=10, 14%). Median time to discontinuation was 134 days (range 21-350 days); 69 days for those who discontinued due to intolerability, and 179 days for disease activity. The patients with and without MS activity on PEG-IFN could not be distinguished in terms of age, duration of disease, or duration or type of prior interferon therapy.

**Conclusion:** The observed high rate of discontinuation of PEG-IFN due to tolerability and MS relapses among previously stable interferon-treated patients was unexpected given the within-class therapy switch. These findings mandate a cautious reevaluation of risks and benefits of switching previously stable interferon-treated patients to PEG-IFN.

### Disclosure

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L Grote holds equity in Roche.

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### EP1734

#### Lack of clinically meaningful changes in cardiac effects from co-administration of ozanimod and a beta-blocker or a calcium channel blocker

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**Background:** Ozanimod (RPC1063) is an oral, selective sphingosine 1-phosphate (S1P) 1 and 5 receptor modulator in clinical development for the treatment of relapsing multiple sclerosis and inflammatory bowel disease (Cohen, 2016; Sandborn, 2016). Initiation of S1P receptor modulators causes transient decreases in heart rate (HR) that decreases with repeat dosing (Kovarik, 2004). The primary objective of this study was to compare the cardiac effects of ozanimod initiation in combination with steady-state propranolol or diltiazem to that of ozanimod alone.

**Methods:** In a double-blind, placebo-controlled, 3-period crossover study, 2 separate groups (propranolol and diltiazem groups) of 18 healthy subjects each received 3 treatment arms (separated by 7-10 days) per randomly assigned sequence: 1) placebo for 5 days and a single dose of ozanimod 0.25 mg on Day 5; 2) propranolol 80 mg or diltiazem 240 mg once daily for 5 days and placebo on Day 5; and 3) propranolol or diltiazem for 5 days plus a single dose of ozanimod on Day 5. HR nadir (0-12 hours postdose) and maximum increase (over a 24-hour postdose) from baseline PR interval were evaluated using least squares mean (LSM) differences ( $\Delta$ HR or  $\Delta$ PR) from a linear mixed model, with fixed effects for sequence, treatment, period, baseline as continuous covariate and subject (sequence) as a random effect. The pharmacokinetics (PK) of individual drugs were evaluated.

**Results:** Administration of ozanimod alone in the propranolol group and diltiazem group resulted in mean (SD) HR reduction from 75.7 (8.12) and 73.8 (11.41) bpm at baseline to 62.7 (7.48) and 63.6 (7.95) bpm at nadir, respectively. Propranolol+ozanimod arm and diltiazem+ozanimod arm resulted in mean (SD) HR reduction from 65.6 (6.61) and 73.9 (9.68) bpm at baseline to 55.2 (5.80) and 61.6 (7.63) bpm at nadir, respectively. Compared to ozanimod alone, a small and not clinically meaningful  $\Delta$ HR (95% confidence interval [CI]) of 0.57 bpm (-1.95 to 3.10) for propranolol+ozanimod or -1.31 bpm (-3.14 to 0.52) for diltiazem+ozanimod was observed. Small, non-clinically meaningful  $\Delta$ PR (95% CI) for (propranolol+ozanimod vs propranolol) and (diltiazem+ozanimod vs diltiazem) were 1.65 ms (-2.98 to 6.27) and 4.53 ms (-5.26 to 14.3), respectively. The PK of individual drugs were not affected during co-administration.

**Conclusion:** Co-administration of ozanimod and propranolol or diltiazem did not result in further clinically meaningful changes in HR or PR interval.

## Disclosure

JL Boyd, Shareholder, Celgene;  
S Walker, Consultancy, Celgene;  
P McCloskey, Shareholder, Celgene;  
M Syto, Shareholder, Celgene;  
JQ Tran, Shareholder, Celgene;  
B. Darpo, Shareholder, iCardiac Technologies.

## EP1735

### Anti- JCV antibody Sero-positivity and index value among Iranian patients with multiple sclerosis and its correlation with demographic data and previous therapies

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**Background:** Anti- JCV antibody index is the predicting factor of progressive multifocal leukoencephalopathy (PML) for multiple sclerosis (MS) patients treating with Natalizumab.

**Objectives:** To evaluate the prevalence of anti-JCV antibody positivity and high index among Iranian patients who are the candidate for Natalizumab to see its correlation with their demographic data.

**Method:** This cross-sectional study assessed all received anti-JCV Antibody test result of Iranian MS patients between Jan 2014 and Dec 2016. Demographic data and disease characteristics were also obtained. After data quality control, statistical analysis was done using logistic regression.

**Results:** Among 803 MS patients that were observed, prevalence of anti-JCV antibody positivity was 67.9% (mean of index=2.23; standard deviation (SD)=1.16) and 67.6 % of positive patients had index  $\geq$  1.5. Males were more anti-JCV antibody positive than females (81.7% and 64% respectively; significance sig. < 0.001, crude OR =2.51, CI: 1.65-3.81). Patients with 50  $\leq$  years old age (y.) comparing to patients with  $\leq$ 18 y. had higher positivity prevalence (sig. =0.021; adjusted OR = 3.45, CI: 1.20-2.86). Patients who lived in cold regions had significantly more prevalence of positivity (Number of cases=403; sig. = 0.043 and crude OR = 1.86, CI: 1.02-3.39) and higher rate of index  $\geq$  1.5 (sig. = 0.017; crude OR=3.99, CI: 1.79-8.88). Disease onset age between 28 to 37 y. were more positive comparing to 18 to 27 y. (N= 480; sig. =0.02; adjusted OR=1.85, CI: 1.09-3.14) but correlated reversely with index (sig. =0.01).

**Conclusions:** Age, male gender, onset age, cold area residency significantly influenced anti-JCV antibody positivity prevalence. Only age of onset and cold area residency related to the index. No significant difference observed between the previous type of disease modifying drugs, dosage and duration of treating with them and anti-JCV antibody positivity and its index.

## Disclosure

Founding source: this study was funded by Tehran University of medical sciences.

Conflict of interest: authors declare no conflict of interest.

## EP1736

### Pregnancy outcomes with delayed-release dimethyl fumarate: interim results from an international registry

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**Background:** Data from clinical trials and post marketing reports show no safety signals with exposure to delayed-release dimethyl fumarate (DMF) during pregnancy; however, these data are limited and the product label recommends use during pregnancy only if the potential benefit justifies the potential risk to the foetus.

**Objectives:** To assess interim pregnancy outcomes in an international registry (NCT01911767) of women with MS exposed to DMF since the first day of their last menstrual period prior to conception or at any time during pregnancy.

**Methods:** DMF-exposed women with MS participating in the registry were prospectively evaluated for live births and pregnancy loss, defined as elective or therapeutic pregnancy terminations, spontaneous abortions, and foetal death including stillbirth. Ectopic and molar pregnancies, birth defects, any congenital anomalies or infant death occurring at  $\leq$ 52 wks of age, and any maternal death at  $\leq$ 12 wks postdelivery, were reported. Baseline data were collected at enrolment; follow-ups were conducted at 6-7 mos of gestation and 4 wks after the estimated delivery date, and 4, 12, and 52 wks after birth. Gestational size (GS) was classified as small (< 10<sup>th</sup> percentile), appropriate (10<sup>th</sup>-90<sup>th</sup>), or large (>90<sup>th</sup>) based on WHO or country-specific growth charts. Potential birth defects were adjudicated by an external teratology expert.

**Results:** As of 30 Sept 2016, 104 patients (pts) were enrolled in the registry; mean (SD) age was 31 (5) yrs. Of the 94 pts with a known DMF exposure date, 95% occurred in the first trimester, 1% in the second, and 0% in the third. To date, 58 pregnancy outcomes have been reported, including 52 pts with 54 live births and 4 (7%) spontaneous abortions (< 22 wks). Of the 54 (93%) live births, 47 (87%) were full term (delivered  $\geq 37$  wks) and 4 (7%) premature. Two (4%) infants had adjudicator-confirmed birth defects: 1 with pyloric stenosis, and 1 with transposition of the great vessels and patent ductus arteriosus. No maternal, neonatal, perinatal, or infant deaths were reported. Of the 40 infants with GS data, 3 (8%) were classified as small, 34 (85%) as appropriate, and 3 (8%) as large.

**Conclusions:** The limited interim results from this ongoing registry did not identify a safety signal for DMF exposure on pregnancy outcomes, consistent with previous reports. Final results will provide essential information for women of childbearing age concerning the safety of DMF during pregnancy.

**Supported by:** Biogen

### Disclosure

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**Nicholas J. Everage:** employee of and holds stock/stock options in Biogen

**Shifang Liu:** employee of and holds stock/stock options in Biogen

**Jang Yun:** employee of and holds stock/stock options in Biogen

**Claudia Prada:** employee of and holds stock/stock options in Biogen

**Jerome Hanna:** employee of and holds stock/stock options in Biogen

### EP1737

#### Acalculous cholecystitis as an infusion-related reaction in alemtuzumab-treated RRMS patients. Long-term follow-up and conversion to chronic disease

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Alemtuzumab is an effective therapeutic option for patients with active relapsing-remitting multiple sclerosis (RRMS). Its adverse event profile mainly comprises development of secondary autoimmune disorders and infusion-associated reactions (IARs). The latter mostly manifests with headache, pyrexia and rash, but also rarely includes hypotension, cardiac arrhythmia, and anaphylactic shock. IARs are usually limited to the first days of infusion and - if managed properly - do not cause sustained impairment.

We recently described acalculous cholecystitis (AAC) as a novel, but rare IAR. AAC itself is usually seen in intensive-care-unit (ICU) patients suffering from septicemia following surgery and in end-stage HIV infections. Furthermore, AAC has been a complication of infectious (e.g. Epstein-Barr virus or cytomegalovirus infection) or inflammatory disorders (e.g. systemic lupus erythematosus, Sjögren's syndrome). Diagnosis is often rendered

difficult due to unspecific symptoms such as upper right quadrant stomach pain, pyrexia and inconclusive laboratory findings (e.g., often normal levels of alkaline phosphatase). Precise treatment is crucial given the high mortality of about one third of patients.

Among the 180 infusion courses that were administered to around 100 patients in our department between 2015 and 2016, we detected 4 cases of AAC. All cases were confirmed using CT and/or ultrasound imaging. In contrast to our previous experience, this condition is not always limited to the first days of infusion and was converted to chronic gall bladder inflammation in two cases. Furthermore, AAC did not occur as a single event and was detectable also after repetitive courses of Alemtuzumab in the three patients that did not undergo cholecystectomy. In one patient requiring cholecystectomy, histopathology demonstrated lymphocyte invasion in the gallbladder.

These findings require careful consideration on whether the appearance of AAC in alemtuzumab patients should lead to subsequent cholecystectomy. Facing the potential risk of chronic gall bladder inflammation, monitoring should include clinical surveillance for this condition. Generally, physicians should be aware of this IAR and seek contact to gastroenterologists or surgeons in suspicious cases.

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### EP1738

#### Rituximab-induced interstitial lung disease in a patient with neuromyelitis optica spectrum disorder: the first case report

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**Introduction:** Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disease of the central nervous system (CNS)



which is predisposed to the optic nerves and spinal cord. Rituximab (RTX) is a chimeric monoclonal antibody to the CD20 in pre-B / mature B cells and has been suggested as an efficient treatment for NMOSD. Its common side effect includes infusion related reactions, fever/chills, infection, and respiratory complications. Among them, RTX-induced interstitial lung disease (ILD) is very rare, but potentially fatal. Herein, we report a first case of RTX-induced ILD in a patient with NMOSD.

**Case presentation:** A 48-year-old woman with NMOSD with aquaporin-4 IgG presented to the hospital complaining of dyspnea and a non-productive cough for 3 weeks. Two months prior to symptom onset, she was treated with four cycles of rituximab therapy. She did not have any signs or symptoms for respiratory disease before RTX treatment. Physical examination showed normal breath sounds on auscultation and normal saturation at rest, nevertheless her pulmonary function test showed a mild restrictive pattern with a reduced diffusion capacity for carbon monoxide of 46% and forced vital capacity of 75%. Chest CT scan also revealed bilateral patchy ground glass opacities with subsegmental linear atelectasis on bilateral lower lobe. The diagnosis of rituximab induced ILD was made on clinical and radiological basis and her RTX treatment was discontinued. Two months after the diagnosis of RTX-induced ILD, her respiratory symptom was improved without steroid treatment and her chest CT were normalized. After 8 month, her respiratory symptoms were completely recovered and the follow up pulmonary function test showed normal FVC and DLco.

**Conclusion:** This is the first report of RTX-induced ILD in patients with NMOSD. This rare complication should be considered in NMOSD patients under RTX treatment, who present with dyspnea and/or cough and without any evidence of infection. As the early diagnosis of RTX-induced ILD might produce a good prognosis, clinicians should be aware of the possibility of this complication in NMOSD patients under RTX treatments.

## Disclosure

All of the authors have nothing to disclosure

## EP1739

### Progressive multifocal leukoencephalopathy during teriflunomide in multiple sclerosis patient: a case report

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**Background:** Teriflunomide (TER), the active metabolite of leflunomide, is prescribed by few years for relapsing remitting MS (RR) as first line therapy (Oh J, 2014). Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS) caused by JC virus primarily seen in immunocompromised patients or associated with specific immunotherapies (Ferenczy MW, 2012). Any case of PML has been reported in patients treated with TER, but two case of leflunomide-related PML has been described. Here, we reported the first case of PML during TER treatment.

**Case report:** A 36-year-old woman with multiple sclerosis, taking TER since three months, on January 30, 2017 developed an acute decline in speech. She was previously treated with natalizumab (N), discontinued after 33 infusions eight months before, for JCV antibodies detection. Brain MRI showed a unilobar area suggestive for PML; cerebrospinal fluid showed JCV DNA (11 copies/ml). A dissemination of brain lesions with several new cortical and subcortical enhancing lesions was observed, making difficult the differential diagnosis between PML-immune reconstitution inflammatory syndrome and new MS relapse.

**Conclusions:** Up to now, there is no knowledge about the possible risk of PML related to immunosuppressant use subsequently N exposure. The acute onset of symptoms, the first unilobar PML lesion documented by brain MRI and low number of CSF JCV DNA copies, support the hypothesis that in our patient PML was in an initial phase at diagnosis time, occurring eight months after N cessation, but few months after TER initiation. However, multiple enhancing lesions occurring without modification of clinical symptoms and without any kind of response to steroid could represent a diffuse MS relapse with exaggerated inflammatory reaction, perhaps related to the underlying not clear mechanism of the drugs. Therefore, this case highlights the debate for a more prolonged PML surveillance program, especially for patients extensively N pre-treated with high risk for PML (Schwab N, 2017) that switch to therapies with an immunosuppressant effect.

**Keywords:** teriflunomide, natalizumab, JC virus, Progressive Multifocal Leukoencephalopathy, safety

## Disclosure

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Dr. Frau serves on scientific advisory boards for Biogen, received honoraria for speaking from Merck Serono and Teva.

Dr. Coghe received speaker fee from Teva and Almirall.

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Dr. Contu, Dr. Barracciu and Dr. Gerevini have nothing to disclose.

## EP1740

### Alemtuzumab-associated anti-glomerular basement membrane antibody-positive glomerulonephritis complicated by secondary thrombotic microangiopathy and posterior reversible encephalopathy syndrome

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**Background:** Potential adverse events associated with alemtuzumab (AL) therapy for relapsing multiple sclerosis (MS) include secondary autoimmune disorders of which autoimmune nephropathies, including anti-glomerular basement membrane (GBM) disease, have been identified in 0.3% of cases. It is unclear if recommended pharmacovigilance for AL involving monthly

blood and urine testing for 4 years from last AL infusion would identify anti-GBM disease in an asymptomatic state.

**Objectives:** To report a rare case of AL-associated anti-GBM Ab positive glomerulonephritis (GN) with unusual complications.

**Case description:** A 30-year-old female with highly active MS was treated first-line with two standard courses of AL (total dose 96mg) 1 year apart. Urine testing and serum creatinine were normal 6 weeks and 3 weeks prior to symptom onset respectively. 5 months after last AL infusion, she presented with a 5-day history of headache, vomiting and oliguria. There was no rash, arthralgia or haemoptysis. Urine showed proteinuria, haematuria and granular casts; serum creatinine was raised (492  $\mu\text{mol/l}$ ). Renal biopsy showed extensive necrotising and crescentic lesions. Anti-GBM Ab titre was markedly raised (463 EliAu/ml). Extensive microbial testing was negative. Cerebrospinal fluid testing was normal.

To date, the patient has been treated with 20 sessions of plasma exchange, 2 courses of rituximab 375mg/m<sup>2</sup>, intravenous methylprednisolone and oral prednisolone with slow taper. 3 weeks from symptom onset, the patient developed fever, headache, visual field defect, severe hypertension and seizures. Magnetic resonance imaging of brain was indicative of posterior reversible encephalopathy syndrome (PRES). Within 24 hours, platelet count dropped to nadir 64X10<sup>9</sup>/l with haemoglobin 8.1g/dl, schistocytes on blood film, increased reticulocytes and reduced haptoglobins, suggestive of haemolytic anaemia. Normal ADAMTS13 activity (70iu/dl) supported a diagnosis of secondary thrombotic microangiopathy. She remains dialysis-dependent with persistently elevated anti-GBM Ab titres (mean 280 EliAu/ml).

**Conclusion:** Failure to detect imminent symptomatic manifestation of AL-associated anti-GBM disease with monthly blood and urine reminds us that although safety monitoring may detect other autoimmune complications such as thyroid disease, it may not identify an explosive onset disorder such as anti-GBM disease. New clinical symptoms should prompt consideration of these disorders.

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## EP1741

### Suspected *pneumocystis jirovecii* pneumonia after alemtuzumab

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**Introduction:** The Food and Drug Administration recommends prophylaxis against *pneumocystis jirovecii* pneumonia (PJP) for patients on alemtuzumab for B cell lymphoma, but not for patients

on alemtuzumab for multiple sclerosis (MS). We present a case of suspected PJP secondary to alemtuzumab immunosuppression in a patient with MS.

**Case report:** A 37-year-old male with a history of MS presented to the emergency room 10/8/2016 with new symptoms of fever, weakness, blurry vision, and shortness of breath. The patient's immunotherapy for MS had recently been switched from natalizumab to alemtuzumab. He received his first alemtuzumab infusion 41 days prior to the onset of these new symptoms. There was a five week washout period between alemtuzumab and his last dose of natalizumab.

Initial infectious workup revealed no abnormalities. There was no leukocytosis, blood cultures showed no growth, and all initial standard viral assays were negative. Spinal fluid studies were within normal limits. Chest X-ray was unremarkable, and magnetic resonance imaging brain revealed no new lesions. The patient was admitted, improved with supportive care, and was discharged with a proposed diagnosis of upper respiratory tract infection 10/12/2016. The patient returned to the emergency department on 10/18/2016 with symptoms of fever, shortness of breath, and non-productive cough. He was found to have exertional hypoxia to the 70's and was re-admitted. Lactate dehydrogenase was elevated to 345 U/L, and CD4 was found to be 36 cells/microliter.

Streptococcal culture, respiratory viral panel, and sputum culture were within normal limits. Computed tomography chest revealed bilateral ground glass opacities. Bronchoscopy was unremarkable. (1 $\rightarrow$ 3)- $\beta$ -D-glucan assay was >500 pg/ml, however gomori methenamine silver stain (GMS) was negative. PJP polymerase chain reaction was not sent. Empiric trimethoprim/sulfamethoxazole (TMP-SMX) and oral corticosteroids were started, and the patient quickly improved. He was discharged on TMP-SMX and was seen as outpatient in both infectious disease and neurology clinic where he was observed to do very well.

**Conclusion:** While GMS was negative in this patient, the clinical picture, elevated (1 $\rightarrow$ 3)- $\beta$ -D-glucan assay, low CD4 count, and improvement with TMP-SMX raise suspicion that this was a case of PJP secondary to alemtuzumab immunosuppression. This case supports the possible need for TMP-SMX prophylaxis in MS patients taking alemtuzumab.

## Disclosure

Elizabeth D Verter: Nothing to disclose

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## EP1742

### Pharmacodynamics and pharmacokinetics of natalizumab administered at extended interval dosing

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**Objective:** To evaluate  $\alpha_4\beta_1$  integrin saturations (SAT) and serum concentrations (CONC) in patients on extended interval regimens of Natalizumab (NTZ).

**Background:** NTZ is approved for every 4-week administration as effective therapy for multiple sclerosis (MS), but carries risk of

progressive multifocal leukoencephalopathy (PML). Extended interval dosing (EID) is being explored in attempt to decrease PML risk. Pharmacodynamics and pharmacokinetics of NTZ at EID are unknown.

**Methods:** Patients who consistently received NTZ on every 6 week EID schedule (EID-6) or every 8 EID schedule (EID-8) for 12 months or more were included. Peak and trough NTZ CONC and SAT were measured using ELISA (Covance) and flow cytometric analysis of whole blood (LabCorp), respectively. Chart review was performed to evaluate disease status.

**Results:** 28 patients were enrolled, of whom 17 were women. Mean age  $\pm$ SD (range) 42.2 $\pm$ 11.5 (20-64). Peak CONC EID-6 121.5 $\pm$ 33.3 (82.6-203.0) and EID-8 114.3 $\pm$ 24.1 (78.9-145.0) ( $p=0.53$ ). Trough CONC EID-6 14.0 $\pm$ 8.9 (0.5-28.8) and EID-8 6.1 $\pm$ 7.1 (0.5-22.9) ( $p=0.02$ ). In EID-6, 55% achieved 'high' CONC (defined as  $>10\mu\text{g/mL}$ ); 39% 'adequate' CONC (defined as 2-10  $\mu\text{g/mL}$ ); and 8% 'inadequate' CONC (defined as  $<2\mu\text{g/mL}$ ). In EID-8, 21% achieved 'high' CONC, 38% 'adequate' CONC; and 43% 'inadequate' CONC. Peak SAT EID-6 91.4 $\pm$ 4.3 (83.8-96.0) and EID-8 92.7 $\pm$ 4.9 (83.7-93.9) ( $p=0.69$ ). Trough SAT EID-6 was 72.1 $\pm$ 11.1 (45.7-87.6) and EID-8 55.0 $\pm$ 24.2 (4.5-87.7) ( $p=0.02$ ). In EID-6, 29% achieved 'high' SAT (defined as  $>80\%$ ); 64% 'adequate' SAT (defined as 50-80%); 7% 'inadequate' SAT (defined as  $<50\%$ ). In EID-8 group, 7% achieved 'high' SAT; 57% 'adequate' SAT; 36% 'inadequate' SAT.

**Conclusions:** Majority of patients on NTZ EID maintained adequate CONC and SAT through increasing dose interval resulted in higher number of patients with "inadequate" CONC/SAT. Analyses of the relationship between NTZ CONC, SAT, and clinical outcomes is planned. This will help understand which CONC/SAT of NTZ is sufficient to exclude entry of auto-reactive T cells into CNS and thereby achieving clinically meaningful response.

## Disclosure

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## EP1743

**Using lumbar puncture to exclude progressive multifocal leukoencephalopathy in people with multiple sclerosis on natalizumab: real life experience in a single centre**

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**Introduction:** These are the principal reasons for lumbar puncture (LP) in people with MS (pwMS) on NTL. Early on, progressive multifocal leukoencephalopathy (PML) can be difficult to

distinguish from a MS based on symptoms and imaging but prompt diagnosis improves clinical outcome. In addition changing therapy from NTL to a treatment where prolonged immunosuppression is expected increasingly drives a need to exclude PML. We studied the reasons for, results from and outcome after LP in those on NTL in our cohort.

**Methods:** We collected clinical and MRI data, serum anti-JC Virus antibody (JCVab) titres and CSF results for pwMS who had LP's performed on NTL.

**Results:** 58 pwMS (64% female) were identified (mean: age 40.95 $\pm$ 9.55, MS duration 3.91 $\pm$ 2.24, anti-JCVab titre 2.05 $\pm$ 1.41). Compared to the total cohort of pwMS on NTL the only difference was in the mean anti-JCVab titre ( $p<0.0001$ ). Of the three indications for LP worsening symptoms was the reason in 20 (new lesions: 2, PML: 2), medication change in 29 (new lesions: 6, PML: 0) and new lesions in 9 (PML: 0). The total number of patients with new lesions was 17 (29.3%), comparable to the total cohort ( $p=0.13$ ). Worsening symptoms had a positive predictive value (PPV) for developing PML of 10% (95% confidence interval (CI) 7.06%-13.98%); new lesions PPV of PML of 5.88% (95%CI 1.45%-20.98%) and changing medication PPV of PML of 0%. Analysis of the LP results found that there was an increase in white cell counts in JCV-DNA positive cases versus JCV-DNA negative cases ( $p=0.002$ ). After LP, 13 remained on NTL, 30 changed medication and 13 stopped all treatment. Two pwMS developed PML and both survived.

**Discussion:** Though the emphasis on monitoring focuses on the specificity of new lesions in the diagnosis of PML in this cohort new lesions were a common finding on NTL but did not in isolation have a high PPV for PML. The most important feature was new symptoms.

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## EP1744

**Type 0 blood group associates with higher anti-JCV antibody levels**

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**Background:** JC virus (JCV) associated progressive multifocal leukoencephalopathy (PML) occurs during therapy for multiple sclerosis (MS). Detection of anti-JCV antibodies, and the so-called serum "index values" are accepted risk factors for the later development of PML. The reasons why higher antibody levels to JCV associate with higher risk of developing PML are not well understood. Host genetic factors may influence the anti-JCV antibody levels, and thus may be the underlying cause for such link. Putative host gene candidates could include those that encode the ABO blood groups, with the blood group 0 previously noted to display a trend for over-representation in cases with PML (Khoury et al, JAMA Neurology 2013).



**Aim:** To assess if type O blood group associated with higher levels of anti-JCV antibodies, and if type O blood group therefore was a risk factor for the development of PML.

**Methods:** Determination of ABO blood group antigens on blood samples of 62 patients with PML, and 64 controls without PML. Sera were tested in an enzyme-linked immunosorbent assay using a JCV-VP1 protein fused to GST as antigen, and anti-JCV antibody levels in arbitrary units (AU) were determined as previously published (Warnke et al, MSJ 2013).

**Results:** Of the patients with PML and known underlying disease, 62% were patients with MS treated with natalizumab, 14% were HIV positive, and 11% had underlying malignancy. JCV antibody levels were higher in patients with blood group 0 compared with all other blood groups, irrespective of the development of PML (0: median AU: 136; not 0: median AU: 53;  $p < 0.01$ ). This association was not observed for the closely related BK virus. Of the 62 patients with PML, 29 (47%, 95% CI 35-59%) were of blood group 0, which showed a non-significant trend to differ from the expected distribution in the German population (41%), and the MS controls studied (23/64=36%, 95% CI 25-48%). In the natalizumab-associated PML subgroup, this deviation was the most prominent with 16 of the 29 cases having blood group 0 (55%, 95% CI 38-71%).

**Conclusion:** The ABO blood group 0 antigen associates with higher anti-JCV antibody levels, and may impact the risk of the later development of PML. The non-significant over-representation of blood group 0 in cases with PML was in line with a previous publication. Larger studies are warranted to assess a potential value of host genetic risk factors, such as the ABO status, for PML risk prediction during immunotherapy.

## Disclosure

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## EP1745

### Low signal intensity rim on magnetic susceptibility imaging in patients from the Dutch-Belgian natalizumab-associated PML cohort

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**Background:** Brain magnetic resonance imaging (MRI) plays a crucial role in the diagnosis and follow-up of natalizumab-associated progressive multifocal leukoencephalopathy (NTZ-PML)

patients. Recent studies have demonstrated that PML lesions may show a low signal intensity (LSI) rim or band along the grey-white matter junction on susceptibility weighted imaging (SWI) or T2\*-weighted imaging (T2\*WI), which is likely caused by iron accumulation in macrophages in the lower layers of the cortex.

## Objective:

To investigate whether the presence of a LSI rim on SWI or T2\*WI is a reproducible finding in patients from a multi-center, real-world, and heterogeneous, dataset of local and referred NTZ-PML patients.

**Methods:** Patients were collected from the ongoing Dutch-Belgian NTZ-PML cohort and included in the study if a MRI with SWI or T2\*WI sequence was available after the diagnosis of PML. The image acquisition was not standardized and based on local scanning protocols. Two raters in consensus scored the presence of a LSI rim, its location and whether it was located in, or adjacent to, a PML lesion.

**Results:** Of the 30 screened patients, 8 patients were included. A total of 10 MRIs (five different MR scanners; three 1.5T and two 3.0T) with SWI (n = 7) and/or T2\*WI (n = 7) were available. The MRIs were performed at the acute PML stage (n = 2), PML-immune reconstitution inflammatory syndrome (IRIS) stage (n = 2), and chronic/follow-up stage (n=6).

In 7 of the 8 patients a LSI rim was visible (7 out of 10 MRIs): 2 in the acute PML stage and 5 at the chronic stage. The LSI rims were observed in the left frontal lobe (n = 3), right frontal lobe (n = 4), or left occipital lobe (n = 1), and all were in or adjacent to a PML lesion.

**Conclusion:** We show that the presence of a LSI rim was observed in, or adjacent to, a PML lesion in 7 out of 8 patients tested. This suggests that SWI and T2\*WI may add to the diagnosis and follow-up of PML without being influenced by differences in image acquisition.

## Disclosure

MTW does not report any potential conflict of interest.

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## EP1746

### Understanding the treatment preferences of people with relapsing remitting multiple sclerosis

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**Background:** The last decade has seen a large increase in the number of disease modifying treatments (DMTs) for people with relapsing remitting multiple sclerosis (PwRRMS). There is, however, a knowledge gap as to which type of DMT people prefer, how their choices are related to treatment attributes (how aggressive they are, risks, mode of administration, etc.), and how these

preferences relate to when/if treatments are started. Discrete choice experiments (DCEs) help to understand the relative importance of treatment attributes and the trade-offs made in decision-making but they need to be supported by robust qualitative work.

**Aim:** To identify which are the attributes of DMTs attributes most important to PwRRMS as a first step to design a DCE.

**Methods:** Attribute identification included 3 phases:

- 1) A critical review of the literature to generate a conceptual framework for setting out the underlying context in which behavioural decision making takes place.
- 2) Stakeholder focus groups (n=17 participants) with PwRRMS, neurologists and MS nurses to explore preferences for individual DMTs, their benefits and risks, and to establish a sampling strategy.
- 3) Semi-structured qualitative interviews with PwRRMS (n=30) to understand the main factors that discourage and encourage choosing, starting, switching and stopping DMTs; why such decisions are taken, and how specific preferences relate to attributes of the DMTs. Data was analysed using a thematic analysis.

**Results:** Eight key interrelated attributes of DMTs were identified:

- 1) mode of administration;
- 2) effectiveness;
- 3) duration, severity, controllability and reversibility of side effects;
- 4) how treatment routine - including frequency of administration and side effects management- fits into lifestyle;
- 5) practicality & transportability;
- 6) treatment monitoring;
- 7) likelihood of adherence;
- 8) parenthood and reproduction.

**Conclusion:** PwRRMS trade off a complex set of interrelated attributes to weigh up advantages and disadvantages of DMTs. Some of them are related to DMT clinical outcomes (efficacy, side effects) whilst others are related to how DMT outcomes and processes can be integrated into patients' lives.

## Disclosure

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Schmierer, K is the PI on trials sponsored by Novartis, Roche and Teva and is involved in trials sponsored by Biogen, Genzyme, BIAL, Cytokinetics and Canbex. He has received speaking

honoraria from, and/or served in an advisory role for, Biogen, Novartis, Teva, Merck Inc. He was supported by Genzyme to attend AAN 2014 and Novartis to attend AAN 2016. He has received research support from Novartis, Biogen, National MS Society (US), MS Society of Great Britain & Northern Ireland, Royal College of Radiologists, and Barts Charity.

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## EP1747

### Behçet's disease following alemtuzumab treatment for multiple sclerosis

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We report the case of a 41-year-old female with relapsing-remitting multiple sclerosis. Six weeks following her second treatment with alemtuzumab she developed recurrent genital and mouth ulceration. The results of a serum auto-immune and vasculitis screen were unremarkable and biopsy of the lesions showed epidermal ulcerations.

On the first occasion, her ulcers improved with oral steroid treatment over five days. Two further recurrences responded well to the use of topical steroids.

The occurrence of these skin manifestations appeared to be related to treatment with alemtuzumab and the patient met the clinical criteria for the diagnosis of Behçet's disease. To our knowledge this is the first reported case of alemtuzumab therapy followed by Behçet's disease.

## Disclosure

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David Cottrell: has previously accepted speakers fees and/or hospitality from Serono, Biogen, and Novartis.

## EP1748

### Safety issues in multiple sclerosis patients treated with alemtuzumab in real world

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**Introduction:** Alemtuzumab is a monoclonal antibody used as induction or escalation therapy in patients with multiple sclerosis (MS). The most frequent adverse events happened in the first months.

**Objective:** To study the adverse events in the first months of treatment with alemtuzumab in MS patients in real world.

**Methods:** Observational study. We study patients with multiple sclerosis, who received at least one cycle of alemtuzumab and were followed at least six months. Blood and urine tests were performed at baseline, three and five days after the start and later monthly.

**Results:** 20 patients with RRMS (16 females, mean age 43 ) with and baseline EDSS of 5.5 ( 2.5-7.0) were studied.

The most frequent adverse event during the infusions was mild to moderate rash. Interestingly, in 80 % of the patients there was a transitory increase of liver enzymes (between 2- and 5-fold the upper limit of normal, ALT maximum 196 u/l) between the third and the fifth day of the infusion in 80 % of the patients. One patient with 10 times elevation of ALT and AST presented an acute abdominal pain, the treatment was discontinued and the liver enzymes were normalized after two weeks. Hepatitis C and B were discarded. Other adverse events in the first week were fever (40%), headache (35%), fatigue (10%).

During the first month three patients suffered from unfrequent infections produced by *Listeria monocytogenes*, by *blastocystis hominis* and by herpes zoster. After the adequate treatment were solved without sequelae.

**Conclusions:** Most frequent adverse events with alemtuzumab were cutaneous rash and liver enzymes elevation in the first week. Some not common infections appeared in the first month. Monitoring of infections in the first month is needed. Vaccinations or antibiotics could be useful in some patients to reduce the number and severity of infections.

## Disclosure

Celia Oreja-Guevara has received honoraria for speaking and/or consultancy from Biogen, Genzyme, Bayer, Merck, Roche, Teva and Novartis

## EP1749

### Management of infusion related reactions associated with alemtuzumab in patients with multiple sclerosis

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**Background and aims:** Infusion-associated reactions (IARs) occur in >90% patients with multiple sclerosis (MS) treated with alemtuzumab. We aimed to investigate modified premedication scheme consisting of 1g/day of IV methylprednisolone throughout all 5 days of alemtuzumab treatment.

**Methods:** This was retrospective chart review of 38 consecutive MS patients who were treated with alemtuzumab from June 2015 till February 2017 at Department of Neurology, University Hospital Center Zagreb, Croatia and Department of Neurology, University Medical Centre Ljubljana, Slovenia.

**Results:** Seventeen patients (44.7%) did not experience IARs. Skin reactions and fever were the most common IARs attributed to alemtuzumab infusions and they were most frequent on Day 5 and Day 1, respectively. We have observed significant differences in the occurrence of fever ( $p=0.005$ ) depending on the site of

alemtuzumab administration which could be explained by different antipyretics used; fever was absent in the Slovenian cohort because high dose intravenous metamizole was administered. In the Croatian cohort, in 3 patients IARs resulted in hospitalization, in all 3 cases due to worsening of preexisting neurological deficits associated with fever (in one patient paraparesis and in 2 patients cognitive dysfunction). In the Slovenian cohort in one patient the 5 cycle was administered with a 3 days delay due to rash. Two out of 9 treatments naïve, and 19 out of 29 patients who previously received immunomodulatory treatment had IARs ( $\chi^2=5.208$ ,  $p=0.022$ ).

**Conclusion:** Modified premedication scheme consisting of 1g/day of IV methylprednisolone throughout all 5 days of alemtuzumab treatment leads to reduction of IARs, especially skin reactions.

## Disclosure

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BB: Reports no conflict of interest.

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MKS: Reports no conflict of interest.

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## EP1750

### Neurologists' tolerance to risk and uncertainty in the practical management of multiple sclerosis

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**Introduction:** The current treatment landscape in multiple sclerosis (MS) includes the acceptance of potential risks of lymphopenia and elevated liver transaminases with some disease-modifying therapies. Physicians' tolerance to risk is a new paradigm that may influence therapeutic decisions under uncertainty in MS care.

**Objectives:** To assess physicians' tolerance to three specific therapeutic decisions under uncertainty: 1) risk of lymphopenia, 2) risk of elevated liver transaminases, 3) willingness to discontinue treatment for patients who remained stable (neither clinical nor radiological activity) over 10 years.

**Design:** Overall, 25 neurologists completed a survey regarding the optimal management of 20 simulated case-scenarios, their willingness to accept risks of lymphopenia and elevated transaminases for effective MS therapies, and treatment discontinuation for longstanding stable patients. We used the 'physicians reaction to uncertainty', a validated scale to assess neurologists' tolerance to uncertainty.



**Results:** Overall, 60% of participants had low tolerance to uncertainty (mean score 22.5+/-7.9). Participants were more likely to accept a 10% risk of lymphopenia (mean score 86.4+/-11.1%) compared to the risk of elevated transaminases (mean 28.8 +/-19) ( $p < 0.0001$ ). Most of participants were not willing to stop MS treatment even when simulated-cases were stable for over 10 years (mean score 21.2+/-23.1). Multivariable analysis revealed that women neurologists were less likely to accept the risks associated with elevated transaminases ( $p=0.024$ ) and treatment discontinuation ( $p=0.005$ ) despite having similar tolerance to uncertainty score compared to men.

**Conclusions:** Neurologists caring for MS patients have low tolerance to the risks of transaminitis and are not willing to accept treatment discontinuation for longstanding stable patients.

### Disclosure

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Angel Perez Sempere and Maria Terzaghi: nothing to disclose.

### EP1751

#### Impact of a community pharmacy-based information protocol on multiple sclerosis patients' adherence to treatment with dimethyl fumarate: TECPHIE, a randomized study vs usual practice

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**Introduction:** Dimethyl fumarate is an oral compound indicated for the treatment of adult patients with relapsing remitting multiple sclerosis. Adherence to treatment may be impacted by the route of administration as well as side effects. Although the neurologist remains the primary point-of-contact for MS patients, the retail pharmacist has the opportunity to play a key role by providing individually tailored information at the beginning of treatment. The TECPHIE study aims to assess the impact on adherence of motivational interviews provided by community pharmacists in France.

**Materials and method:** TECPHIE is a 12-month, randomized, prospective multicentre study examining two groups of pharmacists: one providing periodic motivational interviews in addition to the usual drug delivery, and one delivering drug in the standard manner. Motivational interviews consist of discussions of different topics in response to patient requests (information about treatment, side effects, or disease; and advice for daily living). The primary criteria for evaluation is the Medication Possession Ratio (MPR) at 12 months. Several secondary endpoints will be evaluated, such as persistence to treatment, use of medical resources,

patient satisfaction with treatment measured by the TSQM (Treatment Satisfaction Questionnaire for Medication), and patient satisfaction with pharmaceutical interviews. The required patient sample size of 150 (75 per group) was calculated based on an estimated adherence of 70% in usual care and an increase of 15 to 20% in interview group.

**Results:** Recruitment began in December 2016. At present, 35 pharmacists have been recruited and 24 patients enrolled. Baseline results will be presented.

**Conclusion:** This study will be able to rigorously assess the impact on adherence of information provided by pharmacists to adult patients with relapsing remitting multiple sclerosis treated by dimethyl fumarate.

### Disclosure

Yves Michiels: member of the scientific committee of the TECPHIE study and investigator of the study, he has received honoraria for it from Biogen France SAS; Novartis, MSD

Patrick Tilleul: member of the scientific committee of the TECPHIE study, he has received honoraria for it from Biogen France SAS;

Hubert Méchin: employees of Observia, which has a research consultancy agreement with Biogen France SAS;

Florence Hammes: employee of Biogen France SAS.

### EP1752

#### Listeria monocytogenes meningitis after course of alemtuzumab for relapsing-remitting multiple sclerosis - a case report

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**Background:** Alemtuzumab (ALM) is a humanized monoclonal antibody approved for the treatment of patients with active relapsing-remitting multiple sclerosis (RRMS). Treatment with this agent may be accompanied by some serious complications. Following this treatment, another autoimmune disease can develop and infectious complications of varying severity can also occur. The present case report describes the development of listeria monocytogenes meningitis in a female patient following a course of ALM for multiple sclerosis.

**Case report:** A 28 year old female of Caucasian race with RRMS developed a fever up to 40 degrees Celsius, headache, vomiting and global weakness several days after a course of 5 infusions of ALM. At neurological exam the signs of meningeal irritation were found and lumbar puncture showed hyperproteinorrhachia (1,098 g/l), elevated cells (72 in 1 ml) and also elevated level of lactate (6,95 mmol/l). PCR DNA of listeria monocytogenes in the CSF was positive. After treatment with ampicillin and cefotaxim the further course of this complication was favourable and patient was discharged home in stabilized clinical status within 17 days.

**Discussion and conclusion:** Listeria monocytogenes meningitis is a bacterial infection. Its source is usually contaminated food. Patients who have received ALM may be more vulnerable to this infection due to changes in the immune system (depletion in both innate and adaptive immunity, which can facilitate the breakthrough of pre-existing clinically silent and CD8+ T-cells

modulated infection with *listeria monocytogenes*). Thus, increased clinical alertness is essential for correct diagnosis and management of this condition. Patients should be also advised to avoid a “risky” food (like meat without heat adjustment, soft cheeses, fresh food from the market, non-pasteurised food etc.) several weeks before and after course of ALM.

### Disclosure

none of the authors has anything to disclose

### EP1753

#### CD62L as a PML risk stratification marker: a 4 years prospective study

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**Background:** Progressive multifocal leukoencephalopathy (PML) is a major concern when using biotherapies for multiple sclerosis (MS) treatment. PML is frequent with natalizumab (NTZ), considered as rare with fingolimod (FGL). Current guidelines on how and when to switch treatment in patients at high PML risk are expert based. They allowed to minimize PML risk but not to avoid new PML cases. Recent studies highlighted the use of the low level of CD62L (L-selectin) (< 10%) as a predictive biomarker of further PML development in NTZ-treated MS patients (Schwab et al., 2013; Pignolet et al., 2016).

**Objectives:** To evaluate and confirm the 10% threshold of CD62L as a PML risk stratification biomarker (PRSB) in NTZ and FGL treated MS patients at high PML risk.

**Methods:** We are using the Best-MS cohort (NCT01981161), a multicentre, observational prospective study conducted to evaluate CD62L as a PRSB. CD62L was monitored by flowcytometry every 3 months for NTZ and 6 months for FGL on CD4 T cells derived from frozen/thawed PBMC. Patient inclusion criteria included: -a- more than 18 months under NTZ or FGL, positive for JC virus serology with -b- an index value (IV) higher than 0.9 or -c- prior immunosuppress. CD62L determination was centralized in only 1 laboratory (Toulouse). We proposed to stop NTZ or FGL only when under 10% of CD62L. A collegial decision on how to switch was performed. All patients signed an informed consent.

**Results:** Started in 2013 and currently by March 2017, 353 patients have been included with 311 under NTZ and 42 under FGL. None of the FGL treated patients experienced a CD62L < 10%. In the NTZ-treated group, only 3.6 % of the patients experienced a low level of CD62L (< 10 %). All patients have been switched to another drug: mean follow-up before switch = 19.6 months ; 9 % to FGL, 50 % to Rituximab, 35 % to Tecfidera and 6 % to Alemtuzumab).

Currently, no PML case was observed.

**Conclusions:** So far, in this cohort, no new PML case was observed. Thus, this prospective study is a first confirmation of the interest of CD62L as a PRSB that may be useful in daily clinical practice.

### Disclosure

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### EP1754

#### Severe disease reactivation in two multiple sclerosis patients after natalizumab withdrawal was not halted by monthly administrations of cyclophosphamide - two case reports

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**Background:** Natalizumab (NTZ) is a highly effective disease modifying treatment for Relapsing Remitting Multiple Sclerosis (RRMS) often discontinued for safety issues. Potentially disabling disease reactivations are frequently observed following its cessation, even beyond the pre-treatment period level. Despite data from small clinical studies, there is still no consensus regarding the best treatment strategy to be adopted in order to prevent such phenomenon. We present two cases of severe disease reactivation in two RRMS patients treated with monthly administrations of Cyclophosphamide (Cy) after NTZ discontinuation.

#### Case reports:

Patient 1: a 33 years old woman affected by RRMS since December 2012 started NTZ treatment in April 2013, after two relapses with MRI activity.

Patient 2: a 25 years old woman diagnosed with RRMS in 2009 started NTZ therapy in April 2010, following Mitoxantrone treatment failure. Both patients achieved complete disease remission during NTZ therapy. After respectively 36 and 46 drug administrations they discontinued NTZ due to safety issues and were treated with monthly administrations of Cy (dosage 0,75 gr/m<sup>2</sup>) after a wash-out period of 2 months. Following the fifth Cy administration, patient 1 developed numbness and hyposthenia in her right limbs. A contrast-enhanced (ce.) brain MRI showed a new 21 mm diameter T2 brain lesion with open-ring Gd enhancement in the white matter of left cerebral hemisphere, consistent with a tumefactive demyelinating lesion. Patient 2 experienced generalized seizure, blurring of vision and right hemiparesis after 3 Cy administrations; ce. MRI showed several new T2 hyperintensities and almost 25 contrast-enhancing lesions in the subcortical and periventricular white matter of cerebral hemispheres. Other potential etiologies were ruled out for both patients.

**Discussion:** Severe clinical and radiological disease reactivations were observed respectively 8 and 5 months following NTZ withdrawal, despite Cy treatment starting after a 2 months washout period. Notably both patients achieved disease remission during NTZ treatment. In conclusion, NTZ is a very effective treatment but its clinical use is restricted by potentially life-threatening infective complications and by the risk of disease reactivation following its withdrawal. The latter represents a still unresolved clinical issue for the MS specialist, needing a safe and more “evidence-based” strategy in order to prevent patient’s disability worsening.

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#### EP1755

**A case of listeriosis in a multiple sclerosis patient treated with alemtuzumab: a strict clinical and laboratory monitoring can help to make early diagnosis and avoid related meningitis**

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We report the case of a 21 years old female, affected by multiple sclerosis since June 2016 with a very high clinical and neuroradiological disease activity in the very first months after onset. She was initially treated with natalizumab discontinued due to an allergic reaction. In February 2017 she was then switched to alemtuzumab-ALEM, administered without any adverse event during the five days of infusion. Two days after she complained for fever, vomiting and headache with progressive worsening. She arrived at our E.R. three days later with high fever (39.5 °C) and severe headache. We performed blood tests finding marked leukocytosis (17600 - 97.1% neutrophils and 0% lymphocytes) and CRP increase (158 mg/L). Due to severe headache we performed spinal tap with normal CSF biochemistry and negative bacterioscopic examination. Blood cultures were also performed and empirical antimicrobial therapy was promptly started with a regimen including ampicilline (2 g 6 times daily) and acyclovir (10mg/kg tid). Within the first 24 hours blood cultures revealed the presence of a Gram positive bacterium characterized as *Listeria monocytogenes* the day after. We added Gentamycine 5mg/kg with clinical improvement in 2 days and blood tests normalization in 7 days. This case underlines the importance of a strict clinical monitoring for infections in ALEM patients, especially in the first two months after drug administration. In the presence of fever with respiratory or gastrointestinal symptoms CMV is the most frequently involved pathogen. However *Listeria* represent another infective agent that should be taken into account, even in the very first days after ALEM infusion despite long incubation period, because of a pre-existing colonization of the gastrointestinal tract. An element that, besides routinary laboratory tests, may help the diagnostic process is the collection of a careful history, including food habits, being *Listeria* mainly acquired from some dietary products. ALEM eligible patients should be therefore recommended to avoid, since at least one month before treatment is scheduled, products such as not pasteurized milk and cheese, raw meat and fish. Furthermore they should be instructed to consume in a few days any prepacked and ready to eat food, even if kept in the fridge, and to observe common hygienic rules (such as washing carefully fruit and vegetables before consumption, and hands before eating or preparing meals).

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## EP1756

**Multiple Sclerosis risk perception and risk acceptance for Brazilian patients**

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**Background:** although many drugs are available for treating multiple sclerosis (MS), and many guidelines published to guide physicians on the best therapeutically choice, the practice of medicine is still dependent on human contact and influenced by emotional and personal history of the individual, and thus the perception of disease severity and the risk-taking behavior might change from one culture to another.

**Goals:** To investigate the perception of MS severity in a cohort of Brazilian patients and access their knowledge of the risks associated to natalizumab (NTZ), their willingness to accept the risks associated with hypothetical drug's profiles, and to compare to two previously presented cohorts (Heensen 2010, Germany; Tur 2013, Spain).

**Methods:** We consecutively interviewed 96 patients with relapsing-remitting MS from 2 centres (São Paulo and Goiás) with a standardized questionnaire, aiming to get their impressions about MS severity, the risks resulting from NTZ treatment and the factors involved in risk perception and decision making upon the choice of drugs with hypothetical risk profiles of severe adverse events from 1:2,000,000

(very low) to 1:50 (very high), as previously performed by Tur (Tur 2013). Answers were given as multiple choices or visual analogic scale.

**Results:** mean age and disease duration were 39.3 and 9.1 years, and mean EDSS 2.6. All patients have received at least one disease modifying therapy for MS (20 used NTZ). MS was perceived as a very severe disease (VAS 7.3; 0=not severe, 10=most severe) and the risk of developing progressive multifocal leukoencephalopathy due to NTZ as moderate to high (VAS 5.9, 0=very low; 10=very high). 76% of the patients considered a risk of 1:1,000 or higher impeditive for the use of NTZ. Older age was the only variable associated to higher risk acceptance. When comparing the willingness to receive a hypothetical drug, our patients disclosed a more conservative profile than German (Heesen) and Spanish (Tur) patients.

**Conclusion:** Brazilian patients in these centres perceive MS severity and PML risk associate to NTZ similarly than elsewhere, but their willingness to take risks is more conservative compared to European patients. This should be considered when discussing therapeutic options with the patients and might have an influence in guidelines adaptations to populations with distinctive cultural background

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## EP1757

**Feasibility of online risk-based monitoring by patients: the Natalizumab case**

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**Introduction:** In the Netherlands 11 Disease Modifying Drugs (DMDs) are registered for Relapsing Remitting Multiple Sclerosis (RRMS) and there are more to come. Some DMDs need risk-based monitoring (RM), however uniformity is lacking. We aim to design one channel for all regimens, including alerts and an active role for the patient.

In the Netherlands 1125 multiple sclerosis (MS) patients are monitored by 28 hospitals monitor via myhealthmonitor.eu/msmonitor (MHM), an online, modular, platform where patients receive, enrich and share their data.

In 2013 the Natalizumab screening APP was added to MHM. The The Natalizumab screening APP consists of 16 questions every 28 days, and must be submitted 2 days prior to the infusion of Natalizumab, sends email reminders. The patient submits the list, the MSnurse can screen the answers and can timely postpone the infusion if needed.

**Aims and objective:** This study analyses the feasibility of for RM in a real-life setting.

**Methods:** Five hospitals use the APP in MHM) in 60 RRMS patients since 2013. MSnurses sign up patients and activate the APP.

Patients were between 22-59 years old, 52 females, 8 males and gave consent.

**Results:** 53 patients (92%) submitted 860 screeningslists (range 1 - 53 per individual), participated between 1 - 1561 days (mean 565 days). In range with clinical purpose: 648 lists (75,4%) were submitted the same day or the next day.

In this real-life setting patients start and stop. At data-extraction (16th of May 2017), 27 patients were "on track" (last submission

before or after 19 April 2017). 33 patients were not “on track”. Reasons for were: never logged on (n=6), Natalizumab was stopped (n=13), personal reasons (n=2), unknown (still using natalizumab) (n=10).

**Conclusion:** This real-life setting shows that patients are capable of providing information on line for RM “in time” as needed for clinical purposes.

An APP to serve all different schedules for the different DMD’s seems a valuable tool to develop in risk-based monitoring in RRMS.

## Disclosure

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## EP1758

### How to treat patients after natalizumab discontinuation: the TY-STOP 2 study, an Italian, prospective and multicenter study

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**Background:** Natalizumab (NTZ) is notoriously associated with progressive multifocal leukoencephalopathy (PML) with a global incidence of 4.20 per 1000 treated patients. After 24 courses, patients and physicians decide whether to continue NTZ or not: a previous study (TY-STOP) showed a stopping rate of about 65%.

**Goals:** To describe study design, methods, state of enrollment, and preliminary results of the TY-STOP2 study, aimed to compare the efficacy and safety continuing versus not continuing NTZ.

**Methods:** An Italian, multicenter (8 centres), prospective, observational study, enrolling patients after at least 24 NTZ administrations. Patients underwent clinical evaluation, magnetic resonance imaging (MRI) and John Cunningham virus (JCV) antibodies testing every three months.

**Results:** Recruitment is still ongoing. Up to now 138 patients have been enrolled: mean age at baseline 37.3 years (SD: 10.7); median expanded disability status scale (EDSS) 2.0 (range: 0-6.5); mean disease duration 8.9 years; ARR pre-NTZ: 0.94. 125 patients (90.6%) continued NTZ after 24 courses; 8/13 that discontinued were JCV-positive (on total of positive of 59/138). During the follow-up, 3 patients stopped NTZ after 6 months, 4 after 9 and 2 after 12. A total of 6 patients out of 126 (4.8%) had a clinical

relapse in the first year after 24 courses. Of these, only 1 had stopped NTZ. 8/87(9.2%) patients with available data had an EDSS increase  $\geq 1$  point in the first 12 months (delta EDSS: median 0 (range: -2.5 - 2)) and 1 of these have discontinued NTZ. 5/103 patients (4.9%) showed at least an active MRI during the first 12 months of follow-up and 1/9 of these with available information had stopped NTZ. 11/74 (14.9%) had an adverse event in the first 12 months (1 serious).

**Conclusion:** This descriptive analysis shows a NTZ stopping rate lower (10%) than in TY-STOP (65%), this is probably due to a better known PML management. However, PML is still a serious NTZ adverse event and more alternative drugs are and will become available. This will probably lead to a higher number of switching patients in our, still ongoing, recruitment. Our study will try to identify a possible therapeutic strategy preserving disease stability and preventing the occurrence of PML.

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### EP1759

#### A case report of asymptomatic progressive multifocal leukoencephalopathy

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We report the development of asymptomatic progressive multifocal leukoencephalopathy (PML) in a 24-year-old woman with multiple sclerosis treated with natalizumab. The patient was diagnosed with PML based on characteristic MRI lesions after 27 infusions of natalizumab. She had no neurologic deficits at the time of diagnosis and John Cunningham virus (JCV) was detected at 15 copies/ml (NIH/NINDS, Bethesda, MD, USA). She was initially treated with mefloquine and mirtazapine and remained asymptomatic for three months. The patient later developed worsening MRI lesions related to immune reconstitution inflammatory syndrome (IRIS). At that time, she received intravenous immunoglobulin (IVIG) and high dose intravenous methylprednisone with radiographic improvement of the lesions. Our report illustrates that early detection of asymptomatic PML and its subsequent treatment resulted in a benign clinical course. In consideration of the additional small number of asymptomatic PML cases that have been reported, we conclude that routine MRI surveillance is important for MS patients that are at high risk for developing natalizumab-associated PML.

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### EP1760

#### Favorable evolution post hematologous stem cell transplant after primary central nervous system lymphoma in a multiple sclerosis under natalizumab

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The association between Primary central nervous system lymphoma (PCNSL) and Multiple Sclerosis (MS) treated with natalizumab (N) can be a coincidence. This case is the sixth known. 150

000 MS are treated with N through the world in 2016. The prevalence of PCNSL is 3.3 cases for 100 000 MS treated with N. This number is higher than PCNSL in the general population (1.8 to 3 for 100 000 person).

To report a new case of PCNSL in MS under N treated with hematologous stem cell transplant (HSCT).

**Case report:** A MS was diagnosed in 1997 in a man born in 1970. After interferon beta-1b, N was started in November 2000. The Expanded Disability Status Scale (EDSS) was 3.0. In June 2011, he was hospitalized because of loss of weight, depression, cognitive impairment and headache. Neurological exam revealed psychomotor slackening, instable walking requiring a crutch (EDSS 6.0). Brain MRI showed several flair hypersignals involving right internal capsule with mass effect on ventricle, corpus callosum and left insula, all enhanced. Standard biological exams, Lymphocytes T, B, blood immunofixation were normal. Serologies were negative except for EBV. Because of the mass effect, lumbar puncture was not done. Bone biopsy, thoraco abdomino pelvic CT scan were normal. The brain biopsy revealed PCNSL type B. In October 2011 he underwent HSCT. In February 2012 he was considered in remission. In May 2012 his walk was to 500 meters. Important asthenia persisted with hyperemotivity. At last visit, patient was stable without MS treatment (EDSS 4.0).

In this case, HSCT allowed not only PCNSL remission but also MS remission. HSCT has been proposed to control or even cure refractory cases of MS for several years. This transplant leads reset the pathogenic T cells repertoire thus renewing the immune system repertoire and possibly reinforcing immune tolerance mechanism.

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### EP1761

#### Rebound of disease activity after fingolimod withdrawal: can we predict it?

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**Background:** Although rebounds of disease activity (RA) after natalizumab withdrawal have been widely described, data about a possible reactivation of disease activity in patients treated with fingolimod (FTY) are limited. We analyse those patients of our Department that have discontinued FTY treatment, we describe rebound cases and we try to establish possible predictors.

**Methods:** Retrospective study including patients with Relapsing Remitting Multiple Sclerosis (RRMS) treated with FTY in whom it has been discontinued, permanently or not. We compare patients with RA after FTY suspension and those with no-RA. We describe demographic, clinical, therapeutic and analytical features before and after withdrawal.



**Results:** 20 patients were included, 18 women. Mean age 37.2 years (SD:8.3). The median EDSS at diagnosis was 1 (SD:0.6) and mean relapse rate at first year was 1.35 (SD:0.58). The mean disease duration until FTY was 8.5 (SD:6.1), with mean time under FTY therapy of 33 months (SD:14.3). Mean of annualized relapse rate improvement was 90%. Mean of peripheral blood lymphocytes under FTY therapy was 300/mm<sup>3</sup> (SD:130). Corticosteroids were used during washout period in 70.6% of patients. There were 17 cases of permanent FTY withdrawal, 10 of them with RA. Mean time to RA was 37 days after withdrawal (DS:22.3). No RA was observed in temporary discontinuations. Patients with RA had lower peripheral blood lymphocyte. No association was found with age, body mass index EDSS, disease activity, immediately previous treatment or the reason of discontinuation.

**Conclusion:** RA after FTY withdrawal was common in our experience. Peripheral blood lymphocytes may be one possible predictor. Future studies are needed for better defining this hypothesis and other intercurrent factors.

### Disclosure

No author has nothing to disclose

### EP1762

#### Central and peripheral nervous system inflammation disease secondary to alemtuzumab therapy

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Alemtuzumab is a pan-lymphocyte depleting anti-CD52 antibody approved as escalation therapy for patients with multiple sclerosis (MS) with clinically or image defined active disease. It has been shown effective in reducing relapse rate and brain volume loss. However concerns have been raised due to its numerous adverse effects. We report a case of severe nervous system inflammatory response following Alemtuzumab infusion.

On March 2017 a 31-year-old woman was referred to our service due to an acute deterioration of her mental status. She had been diagnosed with multiple sclerosis in 2007 after attacks of dizziness and left hemiparesis with typically disseminated T2 lesions fulfilling diagnostic criteria on magnetic resonance imaging (MRI) and oligoclonal band (OCB) positivity on cerebrospinal fluid analysis. Despite the use of several immunomodulatory therapies - interferon beta-1a, glatiramer acetate, cyclophosphamide and natalizumab - the patient maintained frequent relapses and persistent disease activity on MRI. Alemtuzumab was first infused in January of 2017 and in March 2017 the patient presented with severe trigeminal neuralgia, marked cognitive impairment including apraxia and left-dominant tetraparesis. The MRI showed two new lesions on T1 weighted image with ring contrast enhancement in periventricular white matter, thickening and enhancement of nerve roots in bulbar (V, VII and XI nerves) and cervical segments. Infection was ruled out and the patient received 5000mg of methylprednisolone which led to marked clinical and radiological improvement.

The reported case illustrates an exacerbated inflammatory response observed after Alemtuzumab infusion. The response seen in our

patient is consistent with the time-frame in which B-cell repopulation and peripheral expansion occur following alemtuzumab treatment, therefore further cases might be identified. As such, we suggest that apparent relapses after alemtuzumab treatment should be promptly screened by MRI for the presence of therapy-related inflammation.

### Disclosure

Nothing to disclose

### EP1763

#### The first reported case of autoimmune hepatitis following alemtuzumab therapy for multiple sclerosis

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A 43 year old Caucasian female developed a subacute hepatic illness 12 months after completion of her second course of Alemtuzumab for Multiple Sclerosis. This is the first reported incidence of this unexpected outcome.

Multiple Sclerosis was diagnosed in December 2014 following episodes of sensory disturbance and gait ataxia in July and September 2014. Paraclinical findings were typical. Past history included depression and Vitamin D deficiency; a broad autoimmune screen was initially negative.

The patient underwent her first 5 day infusion of Alemtuzumab (12mg/d with 1gram Methylprednisolone on d1-3) in March 2015 without significant difficulty and had her second 3 day infusion in April 2016. Her neurological status only improved with therapy, with no further relapse and increased occupational capacity.

Post-administration the patient manifested a normal time course of lympho-depletion and restitution with mild persisting lymphopenia (0.47-0.94 x10<sup>9</sup>/l). In January 2017 she travelled to Southern India and Thailand, followed the recommended vaccination schedule and experienced no serious illness.

Post-infusion monitoring detected an isolated gradual rise in ALT (163U/l) from March onwards, reaching a peak of 2018U/l by early May 2017 from which time bilirubin and ALP also began gradually rising to peaks of 347umol/l and 269U/l respectively some three weeks later. Clinical features of progressive malaise, steatorrhea, anorexia, right hypochondrial tenderness and jaundice developed contemporaneously with the hyperbilirubinaemia. No coagulopathy or gross encephalopathy arose. The neutrophil count also dropped from normal to 0.38x10<sup>9</sup>/l in March, reaching a nadir of 0.19 x10<sup>9</sup>/l in May 2017.

Broad viral screens were negative. Autoimmune serology returned positive for Anti-LKM. Liver Biopsy demonstrated chronic lymphocytic and plasmacytic infiltrate of portal tracts with interface hepatitis and perivenular necrosis without biliary lesions, fibrosis or cirrhosis. A diagnosis of Autoimmune Hepatitis was made, oral prednisolone 40mg initiated and sustained clinical and haematobiochemical improvement observed. Follow up is ongoing.

## Disclosure

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Mozayani B. Nothing to disclose.

Chelvaratnam U. Nothing to disclose.

Przemioslo R. Nothing to disclose.

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## Tools for detecting therapeutic response

### EP1764

#### Correlation of global and regional brain volume changes with disease activity, cognition and disability in a 2-year follow-up of 60 Finnish MS patients

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**Background:** Brain atrophy occurs in all clinical stages of untreated patients with MS and correlates with disability and cognition at a group level. In clinical trials, high efficacy therapies have shown to reduce rate of brain atrophy. However, brain volume is routinely not measured in normal clinical practice.

**Aims:** To measure global and regional brain volumes in a real life cohort of relapsing remitting (RRMS) and secondary progressive (SPMS) Finnish MS patients. To analyze the correlation of volume changes during 2-years follow-up with cognition and achievement of no evidence of disease activity (NEDA) status.

**Patients and methods:** Global and regional brain volumes was measured from 3D T1 brain magnetic resonance images (MRI) using a Siemens 3.0 Tesla scanner from 24 newly diagnosed RRMS patients 6 months after initiating disease modifying therapy (DMT), and from 36 SPMS patients. Correlation of volumes and volume changes with cognition and disability were analysed using Wilcoxon and Pearson tests with R Statistics. Baseline global brain volume was measured by Sienax and 2-year percentage of brain volume change (PBVC) using Siena. Regional brain volumes were measured by cNeuro (Combinostics Ltd, Finland) using an automated method. SDMT (symbol digit modalities test) was used for cognitive testing and expanded disability status scale (EDSS) for disability measurement. NEDA was determined by no

relapses, no EDSS progression and no new/enlarging lesions of brain MRI.

**Results:** At baseline, mean global brain volumes in patients in RRMS and SPMS groups were 1509 and 1398 ml respectively (Wilcoxon  $p < 0.001$ ). Baseline EDSS was 1.35 in RRMS and 4.61 in the SPMS patients (Wilcoxon  $p < 0.001$ ). EDSS change in 2 years was 0.27 in the RRMS and 0.38 in the SPMS patients. EDSS progression was not significant in either group. There was a moderate correlation with baseline SDMT and thalamic (Pearson  $r = 0.42$ ) and hippocampal (Pearson  $r = 0.38$ ) volumes. Relative change of SDMT at 2 years correlated with thalamic volume change (Pearson  $r = -0.24$ ). NEDA status from the treatment epoch of 6 months after DMT initiation to 2 years thereafter was reached in 35% of the RRMS patients. SDMT worsened in patients not reaching NEDA. PBVC at 2 years was greater in patients not reaching NEDA compared to those reaching NEDA (0.8% vs 0.5%).

**Conclusions:** Thalamic atrophy correlates with cognition in MS. Brain volume loss and cognitive deterioration are greater in patients not reaching NEDA.

## Disclosure

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J Lötjönen is CSO and J Koikkalainen is an employee of Combinostics.

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JO Rinne serves as a consultant neurologist for CRST (Clinical Research Services Turku). The other authors do not have disclosures.

### EP1765

#### Stability of maximal oxygen uptake ( $\dot{V}O_{2max}$ ) and clinical symptoms over one year in multiple sclerosis

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**Background:** Assessment of maximal oxygen uptake ( $\dot{V}O_{2max}$ ) during an incremental exercise test is the gold-standard measure of cardiorespiratory fitness (CRF). Exercise training resulting in improved CRF may be a viable therapeutic strategy to improve MS-related symptoms. Although the association between level of disability and  $\dot{V}O_{2max}$  has been established in persons with Multiple Sclerosis (PwMS), the long-term repeatability of  $\dot{V}O_{2max}$  and its association with changes in other clinical measures is unclear.

**Methods:** Participants in an ongoing longitudinal study completed year 1 and year 2 physical profiles including assessment of EDSS by a neurologist, completion of the MS Impact Scale-29 (MSIS), walking on an instrumented walkway (Protokinetics, Havertown USA) and maximal incremental exercise tests on the total body recumbent stepper with integrated indirect calorimetry.

try system (AEI technologies, Pittsburgh USA) to record cardiorespiratory parameters.

**Results:** Twelve (10F) PwMS aged  $48 \pm 13$  years completed year 1 and 2 assessments. EDSS scores ranged from 0 to 6. At initial assessment:  $\dot{V}O_{2\max}$ , EDSS, MSIS, and walking velocity were  $22.6 \pm 7.7$  ml min<sup>-1</sup> kg<sup>-1</sup>,  $2 \pm 2$ ,  $38 \pm 24$ ,  $103 \pm 30$  cm sec<sup>-1</sup>, respectively. These values indicate low levels of CRF despite preserved walking speed and relatively low levels of disability.  $\dot{V}O_{2\max}$  was strongly correlated with walking velocity, MSIS, and EDSS ( $r=0.87$ ,  $p<0.01$ ;  $r=-0.77$ ,  $p<0.01$ ;  $r=-0.60$ ,  $p=0.041$  respectively), which was maintained at 1-year follow-up ( $r=0.81$ ,  $p<0.01$ ;  $r=-0.82$ ,  $p<0.01$ ;  $r=-0.62$ ,  $p=0.035$ ). No significant changes in  $\dot{V}O_{2\max}$  and clinical measures were observed between time periods. It is important to note that the repeatability of  $\dot{V}O_{2\max}$  over a 12-month period was very high in this cohort with a correlation coefficient of 0.98 and a 95% CI between -0.52 and 1.58 ml min<sup>-1</sup> kg<sup>-1</sup>.

**Conclusion:**  $\dot{V}O_{2\max}$  is associated with clinical measures of MS-related disability and is highly repeatable over a 12-month period in this population. Data collection is ongoing.

## Disclosure

Nothing to disclose.

## EP1766

### The effect of quantitative magnetic resonance imaging (QMRI) on no evidence of disease activity (NEDA) status in multiple sclerosis clinical practice: a multicentre retrospective longitudinal study

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**Background:** Quantitative magnetic resonance imaging (QMRI) is not used routinely in multiple sclerosis (MS) clinical practice, but is regularly used in clinical trials and by some imaging research groups. 'No evidence of disease activity' (NEDA) status is a recent concept that has been examined in few real-world MS cohorts.

## Objectives:

(i) To compare lesion activity and whole brain volume change data obtained by radiologist MRI review with data provided by formal QMRI analysis, performed locally and using MSmetrix;

(ii) To determine whether QMRI analysis data influences NEDA3 and NEDA4 status in this MS cohort.

**Methods:** Clinical brain MRIs (3D T1 and 2D/3D FLAIR sequences) were acquired at baseline and follow-up ( $\geq 12$  months) from 150 MS patients: 50 each from three centres located in Buffalo (USA), Prague (Czech Republic) and Sydney (Australia). MRIs were reviewed by expert neuroradiologists; QMRI analyses were performed both locally and centrally (MSmetrix). Clinical parameters, including relapses and Expanded Disability Status Scale (EDSS) scores, were recorded at both time points. Patients were classified as NEDA3 +/- NEDA4 based on clinical activity/progression criteria combined with MRI activity +/- progression criteria. MRI progression was defined as  $>0.4\%$  (annualised) whole brain volume loss.

**Results:** 150 MS patients (77.3% female; 98.0% Relapsing-remitting MS), mean age  $38.8(10.2)$  years, mean disease duration  $9.0(7.3)$  years and median baseline EDSS 2.0 (range 0-7.0), were evaluated. Based on clinical criteria alone, 65.3% of the cohort were NEDA. With the addition of MRI data from radiologist review, 46.3% were NEDA3 and 45.6% NEDA4. Using local and MSmetrix QMRI data, NEDA3/NEDA4 rates fell to 44.9%/23.8% and 38.8%/19.7%, respectively. Comparison of local and MSmetrix QMRI data revealed discrepancies in the presence of MRI lesion activity and progression in 26.5% and 24.5%, respectively.

**Conclusions:** Incorporating QMRI lesion data had only a modest impact on NEDA3 status in this cohort, which was greater for MSmetrix. Thus QMRI only provides minor additional benefit in NEDA3 assessment over experienced neuroradiologists. However, volumetric QMRI data significantly influenced NEDA4 status, regardless of whether local or MSmetrix QMRI data was used. QMRI is critical for accurate NEDA4 assessment, as relevant brain atrophy rates are not detectable by experienced neuroradiologists.

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**Linda Ly** is an employee of Sydney Neuroimaging Analysis Centre.

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**Robert Zivadinov** has received personal compensation from EMD Serono, Genzyme-Sanofi, Novartis, Claret-Medical, Celgene for speaking and consultant fees. He has received financial support for research activities from Claret Medical, Genzyme-Sanofi, QuintilesIMS Health, Intekrin-Coherus, Novartis and Intekrin-Coherus.

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#### EP1767

##### **Creating a healthcare claims-based adaptation of Kurtzke Functional Systems Scores for assessing multiple sclerosis severity and progression**

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**Background:** Although the demand for observational studies in multiple sclerosis (MS) using real-world data has grown in recent years, administrative codes such as ICD-9-CM do not exist for results of clinical assessment instruments such as the Kurtzke Functional Systems Scores (KFSS). The ability to measure KFSS in healthcare claims databases will improve the capacity to perform comparative effectiveness and safety of medical products studies.

**Objectives:** To map the components of the KFSS to ICD-9-CM codes for identifying MS patients with disease progression and quantifying MS severity.

**Methods:** The KFSS include pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral (or mental) components. As ICD-9-CM does not have all of the exact codes for KFSS signs and symptoms within each system, cross-mapping was performed as close as possible by an experienced clinician and reviewed by clinical informaticists. 'Unknown' (value=9) was not mapped for the KFSS. 'Normal' (value=0) was defined by an absence of a sign or symptom. From the assigned ICD-9-CM code list for KFSS, it was possible to generate Kurtzke Expanded Disability Status Scale (EDSS) scores for patients and to assess disease progression over time. Disease progression was defined by change between the first recorded EDSS score during the first 7<sup>th</sup>-12<sup>th</sup> months of care coverage and the EDSS score during the 1<sup>st</sup>-6<sup>th</sup> months of the patient's most recent 1-year period of care coverage. Change was required to be  $\geq 1.0$  point if the baseline

EDSS score was between 0 and 5 inclusive, or  $\geq 0.5$  point if the baseline EDSS score was  $\geq 5.5$ .

**Results:** From a cohort of 2,960 MS patients, 608 (20.5%) were identified as progressive MS by change in EDSS score. Among these 608 patients, the mean first and second EDSS scores were 0.49 and 4.74. Median (range) first and second EDSS scores were 0 (0-6) and 5 (1-8), respectively. The mean change from the first to second EDSS score was 4.25, while the median was 5 (1 to 7.5). The median KFSS first score for all systems was 0. The mean KFSS first score varied by system, with the highest (1.06) for sensory function and lowest (0.12) for cerebellar functions.

**Conclusions:** Mapping of KFSS using ICD-9-CM can be used to calculate change in EDSS score and identify patients with MS disease progression. Progressive MS patients had a wide range of EDSS score changes with a median increase of 5 during their final year of coverage in the IDN.

#### **Disclosure**

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Schiffon L. Wong is an employee EMD Serono.

#### EP1768

##### **Multiple sclerosis with pattern III lesions successfully treated with mitoxantrone**

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**Background:** In multiple sclerosis (MS) treatment, a personalized approach is pursued to account for the clinical and histopathological heterogeneity. Four different histological patterns of brain lesions were identified: subtypes I and II are characterized by T-cell infiltration without and with antibody involvement, respectively, whereas subtype III and IV reveal a distal or general oligodendrocytopathy, respectively. Apart from pattern II lesions, which have been identified to be predictive for a therapeutic response to apheresis therapies, knowledge about the correlation of histological subtypes and efficacy of treatment regimens is sparse.

**Objectives:** Description of the successful treatment of a MS patient with pattern III lesions.

**Methods:** Case report. Histological and immunocytochemical analysis.

**Results:** A 53-years old male developed atactic gait disorder, dysarthria, and sensory disturbance. Moreover, saccadic pursuits, pallopaesthesia, and pyramidal tract signs were evident. His first MRI exposed a large, contrast enhancing lesion in the left middle

cerebellar peduncle, disseminated supratentorial T2 lesions and a thoracic spinal lesion. Cerebrospinal fluid oligoclonal bands were present. Stereotactic cerebellar biopsy revealed perivascular T cell, macrophage, and plasma cell infiltration, along with demyelination, all compatible with MS. By evidence of oligodendrocyte apoptosis and a significant reduction of myelin-associated glycoprotein (MAG) expression, the lesion was classified as pattern III according to Lucchinetti, Brück, and Lassmann 2000. Treatment with high dose intravenous steroids and 180 mg triamcinolone intrathecally led to recovery of the atactic gait. After immunosuppressive therapy with four cycles of mitoxantrone (12 mg/m<sup>2</sup> body surface) every 2-3 months, his clinical condition and MRI findings further improved.

**Conclusions:** Distal oligodendrocytopathy, MAG loss, and increased hypoxia inducible factor-1 $\alpha$  are common findings in MS with pattern III lesions, but also in virus-induced demyelination and acute white matter stroke lesions. This might indicate a common mechanism based on hypoxia-induced metabolic injury. The treatment response of pattern III lesions to classical immunomodulatory MS therapy is unknown. Since in pattern III lesions a small vessel vasculitis is suspected, immunosuppressive therapies such as mitoxantrone might be more effective and should be considered as therapeutic option.

## Disclosure

Thomas Grüter received a travel reimbursement from Sanofi Genzyme.

Wolfgang Brück serves on the editorial boards of *Neuropathology and Applied Neurobiology* and *Multiple Sclerosis International*. Dr. Brück has received honoraria for lectures by Bayer Vital, Biogen, Merck Serono, Teva, Genzyme, Roche and Novartis and is a member of scientific advisory boards for Teva, Biogen, Novartis, MedDay and Genzyme. He received funding for research projects by Teva, Biogen, Novartis, MedDay and Genzyme.

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Ralf Gold serves on scientific advisory boards for Teva Pharmaceutical Industries Ltd., Biogen Idec, Bayer Schering Pharma, and Novartis; has received speaker honoraria from Biogen Idec, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, and Novartis; serves as editor for *Therapeutic Advances in Neurological Diseases* and on the editorial boards of *Experimental Neurology* and the *Journal of Neuroimmunology*; and receives research support from Teva Pharmaceutical Industries Ltd., Biogen Idec, Bayer Schering Pharma, Genzyme, Merck Serono, and Novartis, none related to this manuscript.

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## EP1769

### Patient reported quality of life and disability measures in the West Yorkshire multiple sclerosis treatment programme

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**Background:** Patient reported outcome measures (PROMs) has been included in recent trials involving both disease modifying and symptom management drugs in multiple sclerosis (MS). There is lack of information on PROMs outside the trial setting in patients treated with different disease modifying treatments (DMT).

**Methods:** All patients with Relapsing remitting MS (RRMS) treated with DMT's including newly licenced drugs prospectively completed Leeds Multiple sclerosis Quality of life (LMSQoL) scale and United Kingdom Neurological Disability scale (UKNDS) on an annual basis. Expanded Disability Severity Score (EDSS) was also assessed during these visits. LMSQoL is an eight item scale with resulting scores from 8 to 32, with higher scores reflecting higher levels of well-being. UKNDS has 12 functional domains with an overall score ranging between 0 (no disability) to 60 (maximum possible disability). Mean scores for LMSQoL, UKNDS during their first 12 months and 24 months were compared to pre-treatment baseline along with the median EDSS.

**Results:** In total we analysed PROMs from 962 patients. There were 595 patients on injectable (Beta-interferon and Glatiramer acetate) treatments, 92 on Natalizumab, 109 on Fingolimod, 151 on Dimethyl fumarate, 7 on Alemtuzumab and 8 on Teriflunomide. In the injectable group there was 2 point increase (p=0.0001) in LMSQoL with small decrease in the mean UKNDS which is not statistically significant with median EDSS remaining stable at 2. In Natalizumab group there was increase of 3.36 points (p=0.0001) on LMSQoL and decrease of 4.89 points (p=0.001) on UKNDS with unchanged median EDSS. In Alemtuzumab group there was 5.81 point increase from baseline (p = 0.07) in LMSQoL, 16.38 decreased from baseline (p=0.007) in UKNDS with 1.5 point reduction in median EDSS. There was no statistically significant change in PROMs in the rest of the treatment groups over the observed 24 month period.

**Conclusion:** There was improvement in the well-being scores from the baseline in people who are on Natalizumab and Injectable treatments. Natalizumab and Alemtuzumab group also reported improvement in their disability.

## Disclosure

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Helen L Ford: In the last year HLF has received consultancy/speaker fees and support to attend educational meetings from Merck, Novartis, Teva and Genzyme

## EP1770

### Whole brain tract disruption better explains cognitive decline in multiple sclerosis than total lesion volume

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**Background:** Total lesion volume is commonly evaluated in multiple sclerosis (MS) as an indicator of overall disease pathology. However, lesion volume often correlates poorly with cognitive

outcomes. Newer techniques allow for the assessment of a global outcome measure which accounts for the number of actual region-to-region connections impaired by individual lesions (based on their location). This measure can be derived from typical clinical MRI and may be better associated with cognitive decline than total lesion volume.

**Objective:** To determine whether whole brain tract disruption caused by lesions is a better predictor of cognitive decline than total lesion volume in MS.

**Methods:** The Network Modification tool was used to quantify tract disruption between gray matter structures caused by white matter lesions in 120 subjects with MS. Linear regressions were used to model cognitive decline with either total lesion volume or whole brain tract disruption, controlling for age and gender. Cognitive decline was assessed via consensus cognitive tests of processing speed, visual memory, verbal memory, and attention (as measured by Symbol Digit Modalities Test, Brief Visuospatial Memory Test-Revised total learned, California Verbal Learning Test total learned, and Paced Auditory Serial Addition Test).

**Results:** For prediction of processing speed, adjusted  $R^2$  was 0.222 for the total lesion volume model and 0.263 for the whole brain tract disruption model - an 18% relative increase in explanatory power

(4% absolute increase). Similar increases in adjusted  $R^2$  were observed in models predicting visual memory (0.120 vs. 0.143), verbal memory (0.147 vs. 0.154), and attention (0.075 vs. 0.083).

**Conclusions:** Although still describing a minority of the variance in cognitive decline, a single measure of global tract disruption is more strongly related to a variety of cognitive deficits in MS than total lesion volume.

## Disclosure

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R Zivadinov received personal compensation from EMD Serono, Genzyme-Sanofi, Novartis, Claret-Medical, Celgene for speaking and consultant fees. He received financial support for research activities from Claret Medical, Genzyme-Sanofi, QuintilesIMS Health, Intekrin-Coherus, Novartis and Intekrin-Coherus.

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## EP1771

### Persistent total suppression of T follicular regulatory lymphocytes in alemtuzumab-treated multiple sclerosis patients

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**Background:** Alemtuzumab, a humanized anti-CD52 IgG1 monoclonal antibody, almost completely depletes T and B cells from the circulation. The long-lasting clinical efficacy of alemtuzumab has been associated to unique modifications of the cellular immune network during the re-constitution phase, characterized by the rapid reappearance of Treg lymphocytes and by prolonged suppression of Th1 and Th17 lymphocytes. However, cases of severely exacerbated central nervous system (CNS) inflammation following alemtuzumab therapy have been described and explained with an exaggerated B-cell activity.

**Aim:** On the base of these observations, we investigated  $T_{FR}$  and  $T_{FH}$  cell number and percentage at all the RRMS patients treated with alemtuzumab in our MS Centre.

**Results:** We observed two alemtuzumab-unresponsive patients that had a severe disease reactivation 4 and 8 months after therapy, respectively. In both patients, we observed the almost complete absence of T follicular regulatory ( $T_{FR} = CD3^+CD4^+CD127^{dim}CD25^+CXCR5^+PD1^+$ ) lymphocytes in the peripheral blood, while T follicular helper ( $T_{FH}$ ,  $CD3^+CD4^+CD127^+CD25^+CXCR5^+PD1^+$ ) lymphocytes were detectable. In one case, it was possible to analyse the cerebrospinal fluid lymphocytes. B cells represented the 12.5% of all CSF lymphocytes, 40% were CD20- (while 98% of peripheral blood B-cells were CD20+) and displayed high values of physical parameters, suggesting an active state. Moreover, 48% of CSF B cells expressed high levels of CD38 and 61% (versus 4% of peripheral B cells) expressed the activation marker CD83, suggested to play a role in the germinal centre maturation. Interestingly, the complete absence of  $T_{FR}$  was observed in all patients independently of the time-point of sampling. In all the patients, variable percentage of  $T_{FH}$  could be demonstrated.

**Conclusions:** The presence of  $T_{FH}$  along with the complete absence of  $T_{FR}$  suggests an imbalanced  $T_{FH}/T_{FR}$  ratio and, thus, a dysregulated follicular reaction. However, despite the persistent total suppression of  $T_{FR}$  the majority of patients benefit from alemtuzumab therapy. Thus the mismatched reconstitution of B and T lymphocytes allows CNS-autoreactive B cell clones to proliferate without control only in a few patients. Whether this phenomenon is related to a given threshold number of circulating  $T_{FH}$  or implies the presence of other immunological abnormalities merits to be investigated in a large cohort of patients.

## Disclosure

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Gallo Paolo has been a consultant for Bayer Schering, Biogen Idec, Genzyme, Merck Serono and Novartis; has received funding for travel and speaker honoraria from Merck-Serono, Biogen Idec, Sanofi-Aventis, Novartis Pharma and Bayer-Schering Pharma, Teva; has received research support from Bayer, Biogen Idec/Elan, MerckSerono, Genzyme and Teva; and has received research grant from the University of Padova, Veneto Region of Italy, the Italian Association for Multiple Sclerosis, the Italian Ministry of Public Health.

#### EP1772

##### **Evaluating the association between absolute lymphocyte count (ALC) after 6 months of dimethyl fumarate treatment and risk of relapse at one year**

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**Objective:** Examine the relationship between absolute lymphocyte count (ALC) and relapses in relapsing MS (RMS) patients on dimethyl fumarate (DMF).

**Background:** DEFINE and CONFIRM trials showed a 40-50% reduction in relapse rate in patients taking DMF 240mg twice a day, however about 1 in 4 patients had a relapse within two years. Grade III lymphopenia ( $ALC < 0.5 \times 10^3$  cells/ $\mu$ L) developed in 6% of patients in the clinical trials and 11% of DMF patients in our community hospital registry. A recent report showed a positive correlation between ALC and relapses for DMF patients. Here we analyzed data from the Providence DMF registry to determine if ALC at 6 months was correlated with relapse within the first year of treatment.

**Methods:** Patients prescribed DMF for RMS from March 2013 to March 2016 who had ALC values at 6 ( $\pm 1$ ) months and relapse data within one year of starting DMF were included. Poisson regression with the logarithm of time on DMF as an offset was used to analyze the relationship between ALC and annualized relapse rate (ARR). Cox proportional hazards regression was used to estimate the relationship between ALC and risk of relapse. Age, gender, and disease duration were included as covariates in the models. For both analyses, ALC was analyzed as a categorical variable with patients grouped into three ALC tertiles (lowest 33%, middle 33%, and highest 33%) and as a continuous variable.

**Results:** Of the 412 RMS patients in our registry during the study period, 116 patients met the inclusion criteria. Nineteen patients (16.4%) had a relapse within one year of starting DMF. While relapses increased with ALC tertiles (lowest tertile, ARR (SE)=0.07 (0.05), hazard ratio (HR)=reference; middle tertile, ARR (SE)=0.11 (0.07), HR=1.20; highest tertile, ARR (SE)=0.18 (0.10), HR=2.27), this trend was not significant ( $p=0.26$  for ARR,  $p=0.128$  for HR). With ALC as a continuous variable, there was suggestive but inconclusive evidence that higher ALC correlated with relapses (adjusted ARR ratio=1.06,  $p=0.086$ ; adjusted HR=1.06,  $p=0.142$  for every  $0.1 \times 10^3$  cells/ $\mu$ L increase).

**Conclusion:** Our results, although not statistically significant, suggest a potential relationship between higher ALC values and relapse. With a numerically larger cohort these differences may have reached statistical significance.

#### **Disclosure**

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#### EP1773

##### **Towards personalized therapy through extensive longitudinal follow-up using a multidisciplinary data infrastructure for people with MS: a-proof-of-concept study**

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Multiple sclerosis should be featured by an individualized and intense clinical follow-up and multidisciplinary treatment. The construction of composite MS diagnostic/prognostic models combining multiple parameters and the development and evaluation of personalized and effective MS treatments and rehabilitation strategies requires extensive longitudinal follow-up. There is an urgent unmet need for multidisciplinary repositories combining (para)-clinical parameters on different levels together with individualized information like immunological and genetic profiles to investigate multidisciplinary research questions combining multiple parameters. Although many, individually held clinical research databases have been developed over the last few decades, open access to them is limited. Furthermore, the interoperability between these data resources is inexistent, because different types of data is acquired in different ways using different controlled vocabularies, which preclude direct integration. The existing (inter) national MS registers and IT platforms are either strictly observational or focus on disease epidemiology, access to new disease modifying drugs or quality of life priorities of people with MS.

The overall aim of this project, "MS DATACONNECT", is building a multidisciplinary data infrastructure for people with MS that allows extensive longitudinal followup. MS DATACONNECT is an initiative of a consortium of 5 partners involved in MS research, care and rehabilitation. Within this consortium, around 660 people

with MS have been investigated. MS DATACONNECT combines following data: 1° *patient specific data*, 2° *disease specific data*, 3° *treatment strategies*, 4° *paramedical data*, 5° *clinical data*, 6° *patient reported data*, 7° *biological sample specific data*, 8° *patient and sample phenotyping*.

To the best of our knowledge, a data infrastructure that combines as many different types of MS data and parameters is unique. The platform is created in collaboration with Imperial College London, using the OPTIMISE open source software developed for use with MS and integrated with the transSMART platform. MS DATACONNECT focusses on interoperability with other international registries and is involved in the development of a European Network of National MS Registries.

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### EP1774

#### Lateral ventricular atrophy measurements agree better than whole brain measures across centers and measurement techniques

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**Background:** Brain atrophy is a key component of MS and an important predictor of disability, but translation to clinical routine is hindered by methodological challenges, including high variability between different centers and analysis techniques. Lateral ventricular volume (LVV) was recently proposed as a robust, clinically-feasible proxy for whole brain atrophy. However, it has not been established whether different methods of measuring

LVV at different centers are more concordant than whole brain measures.

**Objective:** To compare agreement of whole brain and lateral ventricular volume measurements between different sites and assessment techniques.

**Methods:** Three sites collected baseline and one-year follow-up clinical routine MRI for 150 patients with MS. Sites used local, center-specific methods to produce measures of: baseline brain parenchymal volume (BPV), one year percent brain volume change (PBVC), baseline lateral ventricular volume (LVV), and one year percent lateral ventricular change (PLVVC). All scans were also sent to an independent central lab, where CE/FDA approved software was used to generate independent volume and atrophy measures. Correlation between the sites and the central lab was assessed both across and within sites for each measure. One site did not produce normalized baseline data, and was excluded from cross-sectional analyses.

**Results:** Overall BPV agreement with the central lab across the centers was moderate ( $r=0.63$ ,  $p=0.001$ ). Average within-center BPV agreement, controlling for center-specific bias, was slightly higher ( $r=0.68$ ,  $p<0.001$ ). In contrast, overall LVV agreement with the central lab across centers was very high, ( $r=0.968$ ,  $p<0.001$ ). Average within-center LVV agreement was even higher ( $r=0.981$ ,  $p<0.001$ ). For three-center longitudinal data, overall PBVC agreement was moderate ( $r=0.52$ ,  $p<0.001$ ), as was within-center agreement ( $r=0.57$ ,  $p<0.01$ ). PLVVC agreement was again higher both overall ( $r=0.62$ ,  $p<0.001$ ) and within-center ( $r=0.68$ ,  $p<0.01$ ).

**Conclusions:** Both cross-sectional and longitudinal ventricular volume measurements are more stable across centers and analysis methods than whole brain volume measurements.

### Disclosure

**Disclosure of conflict of interest:** Nothing to declare.

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#### EP1775

##### Real life efficacy and tolerability of teriflunomide: multicentre study in Galicia (TERIGAL)

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**Background:** Teriflunomide is an oral formulation which was approved as first line option for the treatment of Relapsing-Remittent Multiple Sclerosis. Its efficacy and adverse events have been described in randomized controlled trials. Data for regular clinical practice are need. We have been using teriflunomide since July 2015.

**Objective:** Our objective is to describe our initial experience with Teriflunomide in terms of tolerance and clinical effectiveness after 1 year of treatment.

**Patients and methods:** All patients from 7 Clinical Hospitals in Galicia, Spain, who were prescribed Teriflunomide were included, regardless of time on treatment. Basics demographic, clinical data, disability (EDSS scale), number of relapses, adverse events and reasons for discontinuation under teriflunomide were reported.

**Results:** 139 patients (72,7% woman) were reviewed, 36% naive, average age 42,8 years old (+9,2), average anual relapse rate (ARR) 0,7 (+0,7), average EDSS 1,62 (+1,5). 119 and 64 patients complied 6 and 12 months of treatment. Teriflunomide decrease ARR at 6: 0,11 (+0,33) and 12 months: 0,19 (+0,79),  $p < 0,05$ . Disability was stable at 6: 1,61 (+1,4) and 12 months 1,98 (+1,7),  $p > 0,05$ . 60 patients (43,2%) experience adverse events, most common gastrointestinal (30,9%), 2 severe (insomnia, elevation ALT) in the first 6 months. 8 patients (5,7%) stopped the treatment in the first 6 months. In the last 6 months 14 patients (10,1%) related adverse events, most common hair thinning (5%), without severe adverse events. 6 patients stopped the treatment in the last 6 months.

**Conclusions:** The efficacy of teriflunomide in real-life setting was demonstrate by the stability in EDSS and reduce the number of relapses. Teriflunomide has been well tolerated by the majority of patients.

#### Disclosure

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## Treatment of progressive MS

#### EP1776

##### MD1003 (High-Dose Biotin) for the treatment of progressive multiple sclerosis: baseline data and results from a cohort of patients included in a early access program

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**Objectives:** MD1003 (biotin 100 mg three times per day) was granted an early access program called Qizenday® cohort Temporary Authorisation for Use (ATUc) in July 2016, following a named patient use called nominative ATU (ATUn) granted in 2015, by the French National Agency for Medicines and Health Products Safety, for treatment of adult primary (P) and secondary (S) progressive multiple sclerosis (PMS) patients 1 year relapse free. ATUc baseline characteristics at inclusion, and efficacy and safety results from both the ATUn and ATUc, are presented.

**Methods:** The ATUc included 5483 patients (61% female) between 13 July 2016 and 12 January 2017 (SPMS: 3080 [56%]; PPMS: 1524 [28%]; PMS type not reported: 880 [16%]); 2781 patients (51%) already received MD1003 as an ATUn. Further patients are currently included in the ATUc. To date, mean baseline values were: age: 57 years; time from diagnosis: 18 years (SPMS: 21 years; PPMS: 13 years); Expanded Disability Status Scale (EDSS) score: 6.1 (SPMS: 6.2; PPMS: 5.9) and walking distance (WD): 218.1m.

Here we report follow-up changes in EDSS, WD and clinical global impression (CGI) over a period of 1 year.

Further results covering the period until July 13 2017, with additional patients and a longer observation period, will be presented.

**Results:** To date, mean change in EDSS remained stable over 1 year while an increase in WD related to duration of MD1003



exposure was observed. An increased proportion of patients had improved CGI related to MD1003 exposure duration.

Safety data were consistent with the MD1003 summary of product characteristics.

**Discussion:** In this large cohort of patients, the efficacy and safety of MD1003 are consistent with the MS-SPI trial results.

### Disclosure

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Bertrand Bourre serves on a scientific advisory board for Merck Serono and has received funding for travel and honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme and Teva.

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### EP1777

**Characteristics and therapeutic management of patients with primary progressive multiple sclerosis - data from a French multiple sclerosis population-based registry (the Multiple Sclerosis Registry in Lorraine Region)**

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**Background:** No disease-modifying treatments (DMTs) have yet been approved for the management of primary progressive multiple sclerosis (PPMS) patients.

**Objective:** To describe the characteristics and therapeutic management of PPMS patients, using the French regional multiple sclerosis (MS) population-based registry (Registre Lorrain des Scléroses en Plaques, ReLSEP).

**Methods:** Data from patients with confirmed MS, first MS symptoms between 2000 and 2014, at least one medical consultation with a neurologist between 2007 and 2015, and without combined DMTs during at least 3 months were extracted from the ReLSEP database. Following descriptive results focused on patients with primary progressive multiple sclerosis.

**Results:** From the 6090 MS patients registered in the ReLSEP database, 1926 MS patients met all the predefined selection criteria, including 263 (14%) patients with PPMS at initial diagnosis. Among these 263 PPMS patients, 190 patients (72%) received at least one DMT from diagnosis and 73 patients (28%) never received any DMTs.

The characteristics of non-treated and treated patients were respectively as follows: women (53% and 50%), mean age at first MS symptoms (48±10 and 44±11 years), mean irreversible score on the Kurtzke disability status scale (DSS, 2.7±1.1 and 2.7±0.7), and median follow-up duration of patients [8 years (Q1-Q3: 5-11) and 9 years (Q1-Q3: 6-12)]. Among the 190 PPMS patients having received at least one DMT from diagnosis, the first treatments prescribed were mostly non-selective IV immunosuppressant (55%) and interferon/assimilated products (35%). Median first treatment duration was 2 years (Q1-Q3: 1-3).

**Conclusions:** Despite no approved drugs, we observe in real life setting that more than 70% PPMS patients received at least one DMT in the RELSEP population. Mainly interferons/assimilated products and non-selective IV immunosuppressant are prescribed.

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L. Bitoun, Dr PH. Depoortere, D. Pau are employed by Roche.

### EP1778

**Laquinimod regulates inflammatory gene induction in a human model of reactive astrogliosis**

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Laquinimod is an orally-delivered immunomodulator which includes actions on the innate immune system and is in clinical trials for primary progressive multiple sclerosis. Laquinimod crosses the blood-brain barrier and enters the CNS, and recent studies suggest that in addition to peripheral actions, it may also exert its effects via direct modulation of reactive astrogliosis, which increasing evidence implicates as a key regulatory mechanism controlling CNS inflammation. Here, we report that laquinimod strongly impacts proinflammatory gene expression in a

primary human model of reactive astrogliosis *in vitro*. Interleukin-1 $\beta$  (IL-1 $\beta$ ) is implicated in lesion pathogenesis in MS, and is a strong inducer of astroglial reactivity in human cultures. We examined the impact of laquinimod on human astrocytic responses to IL-1 $\beta$  treatment. Notably, we found that IL-1 $\beta$  10ng/ml induced a pro-inflammatory transcriptional pattern in primary human astrocytes, which encompassed induction of inflammatory cytokines, reactive nitrogen species, chemokines, adhesion molecules, matrix metalloproteinases, and inducers of endothelial plasticity and blood-brain barrier permeability, as shown by microarray, QPCR and multiplex ELISA. Importantly, at therapeutic concentrations, laquinimod dose-dependently inhibited IL-1 $\beta$  induction of cytokines including TNF $\alpha$ , IL-6, IFN $\alpha$ , IL-12 and IL-23, inducible nitric oxide synthase, and the matrix metalloproteinases MMP7 and MMP10. Suggesting immunomodulation rather than suppression, laquinimod differentially regulated IL-1 $\beta$ -induced expression of CXC and CC chemokines, inhibiting induction of CXCL1,2,5,6,8 and 10, and CCL8, while potentiating CCL5. IL-1 $\beta$  signals via the transcription factor NF- $\kappa$ B, and suggesting mechanism, laquinimod treatment delayed IL-1 $\beta$ -induced I $\kappa$ B $\alpha$  degradation and NF- $\kappa$ B p65 nuclear translocation. Moreover, compatible with a recent *in vivo* study, our data suggest that laquinimod acts as a ligand for the aryl hydrocarbon receptor (AhR), a potent immunoregulator that restricts NF $\kappa$ B activation via direct interaction with its p65 subunit. Collectively, these data reveal laquinimod as a regulator of the proinflammatory phenotype in a human model of reactive astrogliosis, and suggest that it may act in part via AhR-mediated inhibition of NF- $\kappa$ B activation.

## Disclosure

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## EP1779

### An open label, single arm, phase II futility trial of Domperidone treatment in secondary progressive MS. Results of the first stage of the trial

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**Background:** Secondary progressive Multiple Sclerosis (SPMS) is characterized by slow and relentless worsening of disability independent of relapses. In SPMS multiple pathological processes are contributing to the accumulation of disability. The protein hormone prolactin has been shown in animal studies to have neuroprotective properties and to improve remyelination. We hypothesize that increasing systemic prolactin levels in patients with SPMS may slow disability progression. Domperidone is a generic dopamine D2 receptor antagonist that increases prolactin levels in humans. In this clinical trial, we used the Simon-2-Stage Futility Trial model to investigate the effect of Domperidone treatment on disease progression in patients with SPMS.

**Methods and design:** This trial is a one year phase II Simon-2-Stage Futility Trial. The primary endpoint was clinical worsening defined as worsening by 20% or more on the timed 25 foot walk

between baseline and one year follow-up. Based on natural history and original trial data, we expected 40% of the trial cohort to have clinical worsening. The futility threshold was set at 25% of worsening in the trial cohort, using a type 1 error rate of 5% and 80% power. Domperidone treatment is deemed futile if 12 or more of 30 patients enrolled in stage 1 of the trial have clinical worsening at one year follow-up. In the first stage of the trial, 30 patients with SPMS were treated with 40mg of Domperidone daily for 12 months. Trial Registration: Clinicaltrials.gov NCT02308137

**Results:** Overall 52 patients were screened of whom 35 were enrolled. Five patients terminated the trial early. The median age at baseline of the 30 patients who finished the trial was 54 years, 23 (77%) were female, none of the trial participants were using disease modifying treatments. Median serum prolactin levels (normal range: 0-25 mg/L) increased from 9 (interquartile range: 7-12) mg/L at screening to 92 (interquartile range: 38-140.5) mg/L at one month follow-up. At one year follow-up 8 patients had clinical worsening, significantly less than the historical rate of 40% ( $p < 0.05$ ).

**Discussion:** After the first stage of this two stage trial, fewer patients than expected experienced clinical worsening. Domperidone treatment increased serum prolactin levels in the trial cohort. Domperidone treatment is deemed non-futile at this interim stage of the trial. The trial continues into the second stage.

## Disclosure

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## EP1780

### Effect of MD1003 (High-Dose Biotin) in spinal progressive multiple sclerosis (MS-SPI): EDSS sub-scores

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**Objectives:** The MS-SPI study is a double-blind, randomised, placebo-controlled trial of MD1003 in progressive, not clinically active multiple sclerosis patients (pts) with evidence of spastic paraparesis. It showed a reversal of Expanded Disability Status Scale (EDSS) and/or timed 25-foot walk (TW25) in 12.6% of MD1003 pts vs 0 placebo pts ( $p=0.005$ ) at 12 months (M). Here, we present the main study EDSS sub-score results.

**Methods:** In each of the 154 pts included in the study, EDSS sub-scores were recorded for each functional system (FS): pyramidal (P), sensory (S), cerebellar (C11), visual (V), brainstem (BS), bowel and bladder (BB), and cerebral (Cb). Change in sub-score from baseline at each visit was used to define pts as responders (improved) or worsened, depending on whether the score was lower or higher than baseline.

**Results:** Disability was well balanced in each arm and only a small proportion had major disability (score  $\geq 3$ ), other than for P FS. The most common baseline sub-scores (% of pts affected) were: P: 3-4 (~90%); S: 2-3 (~70%); C11: 2-3 (~70%); V: 0-2 (~60%); BS: 0-2 (~50%); BB: 1-2 (~70%) and Cb: 0-2 (~50%).

P scores were  $\geq 4$  in 36% of MD1003 pts at baseline and 35% at M12, and in 43% of placebo pts at baseline and 53% at M12. Between M9 and M12, 10% of MD1003 pts and 2% of placebo pts were responders, while 6% of MD1003 pts and 13% of placebo pts worsened.

S scores were  $\geq 4$  in 3% of MD1003 pts at baseline and 2% at M12, and in 4% of placebo pts at baseline and 11% at M12. Between M9 and M12, 18% of MD1003 pts and 16% of placebo pts were responders, while 9% of MD1003 pts and 31% of placebo pts worsened.

For other FS, the percentage of pts defined as responders/worsened was similar in each arm. For Cb, BS and V, the majority of pts had no impairment or had mild to moderate disability. For C11 and BB, the majority of pts had symptoms but only mild to moderate impairment. However, BB scores between M9 and M12 showed that 10% of MD1003 pts and 13% of placebo pts were responders and 18% of MD1003 pts vs 27% of placebo pts worsened.

**Discussion:** For P and S scores, these results show an improvement in the MD1003 group and worsening in the placebo group. Improvement in the active arm fits with the positive effect on EDSS and TW25. Pts included in the study exhibited high baseline P and S scores while those of other FS were mild to moderate, and thus had less scope to improve.

## Disclosure

Caroline Papeix has received compensation as a consultant, advisory board member or speaker for Roche, Novartis, Biogen, Teva-Aventis, Sanofi Genzyme and MedDay.

Christine Lebrun-Frenay has participated in scientific boards for Biogen, Merck, Teva, MedDay, Roche and Novartis.

Gilles Defer has received personal compensation for serving on scientific advisory boards for Biogen Idec, Merck Serono, Novartis, Sanofi Aventis, Genzyme and Teva. He has received funding for travel and/or speaker honoraria from Merck Serono, Biogen, Guerbet, Sanofi Aventis, Novartis, Genzyme and Teva. His institution received grants supporting research in his department from Merck Serono, Biogen, Sanofi Aventis and Novartis.

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## EP1781

### Identification of main inclusion criteria of chronic progressive multiple sclerosis clinical trials: a review

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**Background:** During the past two decades, many trials have been undertaken in order to improve our knowledge regarding the underlying mechanism and treatment of chronic progressive multiple sclerosis (CPMS). The latter is an old term which refers to advanced MS and includes both secondary progressive (SPMS) and primary progressive MS (PPMS). A lot of progress has been made in the understanding the pathogenesis and treatment of CPMS.

**Objective:** To review the criteria used by both investigator-led and pharmaceutical sponsored studies to recruit patients for chronic progressive MS trials. The objective of this review is to provide a summary of the different inclusion criteria which need to be fulfilled in order to be screened and recruited into a clinical trial investigating disease modifying therapies in CPMS.

**Methods:** Analysis of chronic progressive MS trials using a the-clinicaltrial.gov website, Medline, EU clinical trials (EudraCT), Cochrane Central Register of Controlled Trials (CENTRAL) and ISRCTN register.

**Results:** 97 studies were included. Among them 17 showed positive results. Regarding subject selection, the age range is mainly between 18 and 65 years and very few studies include patients with an expanded disability status scale (EDSS) greater than 6.5. An important design feature of the majority of trials was the requirement of evidence of recent disease progression to be eligible for the study. This evidence can take several forms, ranging from clinical history, EDSS worsening over a certain period of time, or reduction of a patient's performance using specific assessment tools, for example the 9 Hole-Peg Test or Timed-25-Foot Walk.

**Conclusions:** The main criteria for inclusion in trials of progressive multiple sclerosis is evidence of recent disease progression. However, to the best of our knowledge there does not appear to be a standardized protocol to assess the evolution of a patient's disease course for inclusion in CPMS trials. To overcome this issue, we believe that multiple sclerosis self-monitoring tools should be developed in order to help better assess the patient's disease and its evolution, and to assist investigators' in fulfilling the necessary inclusion criteria for clinical trials.

## Disclosure

Nicolas Dubuisson is an ECTRIMS fellow, which is unrelated to the contents of this publication.

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Benjamin Turner has received travel grants and consultant fees for attending advisory boards from Biogen-Idec, TEVA, Merck-Serono, Novartis and Genzyme.

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Gavin Giovannoni has received compensation for participating on Advisory Boards in relation to clinical trial design, trial steering committees and data and safety monitoring committees from Abbvie, Bayer-Schering Healthcare, Biogen-Idec, Eisai, Elan, Fiveprime, Genzyme, Genentech, GSK, GW Pharma, Ironwood, Merck-Serono, Novartis, Pfizer, Roche, Sanofi-Aventis, Synthon BV, Teva, UCB Pharma, and Vertex Pharmaceuticals.

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#### EP1782

##### **In-depth profiling of immune-regulatory network alterations during sequential treatment with natalizumab and fingolimod - results of the ToFingo successor study**

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Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system (CNS) with a variety of treatment options due to the heterogeneous disease manifestation in patients, demanding personalized treatment with regard to efficacy and response. The ToFingo-successor study profiles in-depth the underlining alterations of the immune-regulatory network during sequential treatment of 15 relapsing-remitting MS patients switching from natalizumab to fingolimod, which were analyzed providing detailed information of cell frequency, activation and functional properties as well as correlation to disease activity via MRI measurements. In the end of the 8-week washout period of natalizumab, detailed immune phenotyping of the peripheral blood (PB) did not reveal any alterations, indicating sufficient disease control. After 4 weeks of fingolimod treatment onset, major drug-related effects such as CD4 T-cell trapping were already fully present. In contrast, B-cell and CD8 T-cell decline is protracted, thus indicating that some fingolimod-related effects occur delayed after treatment onset. Notably, the remaining lymphocytes which are able to overcome fingolimods CCR7-mediated retention to the lymph nodes, display markers of terminal differentiation or effector function, illustrating full functionality for immune surveillance. Although in the cerebrospinal fluid (CSF), frequencies of CD4 and CD8 T-cells remain comparable under both drugs, they display, judged by

HLA-DR, a significantly reduced activation status under fingolimod. In contrast, the effect of fingolimod on **non**-T-cell-populations such as B-cells, monocytes and NK-cells in the CSF is less pronounced compared to natalizumab. Finally, we assessed treatment response based both on relapse rate and cMRI, respectively, clinical non-responder demonstrate decreased and/or delayed efficacy of fingolimod treatment on several key parameters and less pronounced CD49d decrease under natalizumab which might be associated with an accelerated loss of natalizumab efficacy after treatment cessation and therefore to insufficient disease control. Taken together, our data suggests that rapid loss of natalizumab efficacy and delayed effects of fingolimod treatment might be responsible for the increased rebounds observed in some patients during switching.

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#### EP1783

##### **Long-term outcomes in patients with progressive forms of relapsing MS treated with teriflunomide: patient-level data from the TEMSO and TOWER extension studies and the real-world setting**

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**Background:** A significant unmet need exists in the treatment of patients with progressive forms of MS. The phase 3 teriflunomide

studies, TEMSO (NCT00134563) and TOWER (NCT00751881), both showed a significant decrease in risk of confirmed disability progression (~31% with teriflunomide 14 mg). These studies included a small number of patients with progressive forms of relapsing MS (PfrMS; secondary progressive MS [SPMS] with relapses and progressive relapsing MS [PRMS]).

**Objectives:** To analyse individual long-term disability outcomes in patients with PfrMS using data from  $\leq 9$  years' follow-up of TEMSO and TOWER, and to present observational real-world experience from patients with PfrMS treated with teriflunomide.

**Methods:** Patients with relapsing forms of MS were randomized 1:1:1 to receive placebo or teriflunomide 7 mg or 14 mg for 108 weeks in TEMSO or, in TOWER, for a study duration that was variable, ending 48 weeks after the last patient was randomized. Patients completing the core studies were eligible to enter extensions. In the TEMSO extension (NCT00803049), teriflunomide-treated patients continued as randomized; placebo-treated patients were re-randomized to teriflunomide 7 mg or 14 mg. In TOWER, all patients received teriflunomide 14 mg in the extension. In a post-hoc analysis, individual long-term Expanded Disability Status Scale (EDSS) outcomes were analysed and listed descriptively. For patients receiving teriflunomide in the real-world setting, a chart review of patients with SPMS or PRMS receiving treatment for  $\geq 3$  years was performed and their long-term EDSS scores tabulated.

**Results:** TEMSO and TOWER included 122 patients with PfrMS at randomization (SPMS,  $n=60$ ; PRMS,  $n=62$ ); 72 (59.0%) completed the core studies and 66 entered the extensions, of which 41 (62.1%) completed at least 5 years. Baseline median EDSS score for patients with PfrMS was 4; at last follow-up ( $\leq 9$  years), median change from baseline was 0. Over periods of up to 5 years, EDSS scores in patients in the real-world setting (SPMS,  $n=9$ ; PRMS,  $n=1$ ) also remained stable; longer-term follow-up of these patients will be presented.

**Conclusions:** These data from a small number of patients with PfrMS and a good initial response to treatment provide preliminary evidence that teriflunomide 14 mg may be associated with long-term stabilization of disease activity and lack of disability progression in patients with PfrMS. These findings need to be confirmed in larger patient cohorts.

## Disclosure

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**KT and PR:** Employees of Sanofi Genzyme.

**SC and PT:** Employees of Sanofi Genzyme, with ownership interest.

**JL:** Employee of Sanofi.

## EP1784

### Biotin in multiple sclerosis in clinical practice: a cohort of 154 patients

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**Background:** Biotin is vitamin acting as a coenzyme for carboxylases involved in key steps of energy metabolism and fatty acids synthesis and could promote remyelination. One double blind placebo controlled trial showed improvement in a significant proportion of patients with progressive multiple sclerosis (MS). Biotin is available in France in temporary use since July 2015.

**Aim:** To study baseline characteristics and follow up of patients treated with Biotin in Dijon (Burgundy).

**Methods:** We studied all progressive MS treated with biotin for more than 3 months included in EDMUS database. EDMUS is used in Dijon since 2000 and includes patients from burgundy MS center. We calculated number of primary progressive (PP) or secondary progressive (SP) form of MS, mean age and EDSS at biotin initiation, proportion of patients for which biotin was used as add on therapy or with fampyra, number of adverse events, Clinical Global Impression (CGI) Scale assessed by patient.

**Results:** 154 patients were treated with biotin, 114 had SPMS and 40 PP. The mean age at MS onset was 32.0 and 45.6 years respectively. Mean age at biotin initiation was 57.6 years with mean EDSS at 6.9 for SPMS; 61.6 years and 6.7 for PPMS. The mean duration of treatment was 8.8 months. 35 patients had biotin as add on therapy among SPMS and 12 for PPMS. 19 (16.7%) patients with SPMS reported adverse events (skin rash, hyperpilosity, diarrhea, anxiety asthenia, oedema) and 3 (7.5%) patients with PPMS (abdominal pain, diarrhea, constipation). 42% of patients reported CGI= 4, 39.5% CGI< 4, 18.4% CGI>4. 48 (31.8%) patients were under fampyra and 103 (68.2%) without, those under fampyra reported CGI improvement more frequently (56% versus 32%)

**Conclusion:** Despite short treatment duration, biotin is well tolerated, and seems more effective among patients under fampyra.

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## Others

## EP1785

### A case of acute fulminant multiple sclerosis treated with alemtuzumab

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**Background:** Marburg's variant of MS (MVMS) is characterized by acute and extensive demyelination, with a typical monophasic fulminant course usually leading to death within few weeks. There is no standard treatment strategy for MVMS. Usually high dose intravenous steroids represent the first line option followed by plasma exchange or intravenous immunoglobulins. The only data regarding the use of immunosuppressants refer to mitoxantrone and cyclophosphamide, which may slow or even stop the course of the disease.

**Objectives:** We describe the case of a woman who came to our attention for a severe neurological presentation characterized by very rapidly worsening left hemiplegia, vision loss and cognitive impairment. The rapid clinical deterioration, the extensive involvement of periventricular white matter and brainstem and the laboratory data were highly suggestive of an active inflammatory demyelinating disease. A wide spectrum of differential diagnosis were investigated, including acute disseminated encephalomyelitis (ADEM), Balo's concentric sclerosis, neuromyelitis optica spectrum disorders (NMOSD) and others infectious diseases.

**Results:** Following exclusion of other possible etiologies, a diagnosis of Marburg type multiple sclerosis was made. The patient was treated with high dose steroids iv without improvement and then with plasma exchange but she became poorly responsive to verbal and pain stimulation, and developed right hemiplegia associated to focal motor seizures. Considering the high efficacy on relapse rate and disability accumulation in relapsing-remitting MS, treatment with alemtuzumab was started. In the following weeks an improvement of the clinical and MRI picture was observed: the patient became awake, responsive to external stimuli, provided verbal responses and showed initial motor recruitment of the right arm.

**Conclusions:** To the best of our knowledge, this is the first reported case of Marburg type multiple sclerosis treated with alemtuzumab. Although a delayed effect of immunotherapies administered prior to alemtuzumab could not be ruled out, this hypothesis seems unlikely considering the continuous worsening of clinical and MRI picture after more than two weeks from steroids and plasma exchange initiation.

## Disclosure

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## EP1786

### Sleep and fatigue features in multiple sclerosis patients on alemtuzumab treatment

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**Introduction:** Previous prevalence studies suggest that patients with multiple sclerosis (MS) have higher frequency of sleep disorders comparing to healthy controls and that sleep disorders contribute in development of fatigue. However, the impact of disease-modifying therapy (DMT) on sleep of MS patients remains unknown.

**Objectives:** The aim of this study was to determine sleep characteristics in alemtuzumab treated MS patients and correlation between sleep disturbances and fatigue.

**Methods:** Out of 30 consecutive MS patients enrolled, 20 received alemtuzumab (12 females, mean age 40.00 +/- 8.96 years) and 10 (7 females, mean age 40.50 +/- 10.75 years) were treatment naïve. All subjects completed standardized Croatian version of Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), STOP-Bang Questionnaire, Restless Legs Syndrome Rating Scale (RLS-RS), Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale (FSS).

**Results:** No statistically significant difference between treatment naïve and alemtuzumab treated patient group was observed in EDSS (median 1.50 vs 1.25,  $p=0.303$ ). Treatment naïve patients had significantly higher RLS-RS score comparing to alemtuzumab treated patients (median 14.50 vs. 0,  $p=0.014$ ). Also, positive correlation was found between ISI score and MFIS score ( $r_s=0.632$ ,  $p=0.050$ ) in treatment naïve group, whereas alemtuzumab treated patients had positive correlation between ISI score and MFIS score ( $r_s=0.629$ ,  $p=0.004$ ), ISI score and FFS score ( $r_s=0.650$ ,  $p=0.003$ ), PSQI score and MFIS score ( $r_s=0.664$ ,  $p=0.003$ ), PSQI score and FFS score ( $r_s=0.615$ ,  $p=0.007$ ).

**Conclusion:** Results of this study might suggest that alemtuzumab treatment eliminates other factors that contribute in development of fatigue besides sleep disorders. The remaining fatigue present in alemtuzumab treated patients might be more dependent on presence of sleep disorders than fatigue in treatment naïve patients.

## Disclosure

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## EP1787

### No evidence of disease activity in anti-JC virus seronegative patients with early relapsing-remitting multiple sclerosis treated with natalizumab: a prespecified 2-year analysis of STRIVE

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**Background:** Treatment with natalizumab early in the relapsing-remitting multiple sclerosis (RRMS) disease course may improve clinical outcomes. STRIVE was designed to determine the proportion of anti-JC virus antibody-negative RRMS patients initiating natalizumab early in their disease course who demonstrated no evidence of disease activity (NEDA).

**Objective:** To determine the proportion of natalizumab-treated early RRMS patients who achieve NEDA at year 2.

**Methods:** STRIVE is a multicenter, observational, open-label, single-arm study in which NEDA was defined as no Expanded Disability Status Scale (EDSS) progression (24-week-confirmed), no relapses, no gadolinium-enhancing (Gd+) lesions, and no new or enlarging T2-hyperintense lesions. Clinical NEDA was defined as no EDSS progression and no relapses. Continuous variables were analyzed with summary statistics. Categorical variables were analyzed with frequency distributions. *P* values and odds ratios (ORs) were obtained from logistic regression models adjusted for baseline EDSS score ( $\leq 2$  vs  $> 2$ ), age group ( $< 40$  vs  $\geq 40$  years), number of relapses 1 year prior to natalizumab infusion, baseline T2 lesion volume, baseline Gd+ lesions, and multiple sclerosis (MS) disease duration, as applicable.

A Kaplan-Meier analysis was used to evaluate time to disability worsening and time to disability improvement.

**Results:** The intent-to-treat population (N=222) had early MS with mean (standard deviation [SD]) time since MS diagnosis of 1.6 (0.8) years and a mean (SD) EDSS score of 2.0 (1.1). Half (50%) of the patients had not received prior disease-modifying therapies. At year 2, 76 of 171 patients (44.4%) had achieved NEDA (95% confidence interval [CI]: 37.0%-51.9%), and 131 of 181 patients (72.4%) had achieved clinical NEDA (95% CI: 65.9%-78.9%). A higher proportion of patients without than with baseline Gd+ lesions (54.7% vs 31.9%) achieved NEDA at year 2 (OR: 2.89; 95% CI: 1.35-6.18; *P*=0.006). At year 2, patients with baseline EDSS score  $\leq 2$  had a significantly higher chance of achieving NEDA than those with baseline EDSS score  $> 2$  (OR: 2.33; 95% CI: 1.08-5.04; *P*=0.032). At year 2, a higher proportion of patients experienced 24-week-confirmed EDSS improvement than worsening (28.4% vs 14.1%). The serious adverse event profile up to year 2 was consistent with natalizumab's well-established safety profile.

**Conclusions:** These 2-year results support the effectiveness of natalizumab in maintaining NEDA in early RRMS patients.

## Disclosure

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## EP1788

### Capillary leak syndrome in neuromyelitis optica treated with rituximab

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**Background:** Capillary leak syndrome (CLS) is a rare condition characterized by unexplained episodic capillary hyperpermeability due to a shift of fluid and protein from the intravascular to the interstitial space with subsequent hypovolemia, hemoconcentration and hypoproteinemia. It can be idiopathic or secondary to some conditions like infection, malignant disease and some drugs like monoclonal antibodies.

**Objectives:** To report a 61 year-old woman diagnosed with NMO three years before and treated with rituximab (RTX), who suffered a fatal CLS one month after the last drug dose. To our knowledge, it is the first reported case of CLS in NMO patient after rituximab treatment.

**Methods:** 61-year-old woman with Neuromyelitis optica (NMO) diagnosis treated with rituximab was referred to our hospital with severe hypovolemic shock and anasarca. Laboratory data showed a progressive increase in haematocrit (max 56.2%), haemoglobin (max 18.6 g/dl) and white blood cell count with a normal fraction. Total serum protein showed a marked decrease (1.6 g/dl) without proteinuria. She developed a multiple organ failure and died three hours later.

**Results:** We diagnosed the patient as having capillary leak syndrome (CLS) because of the hypovolemic shock with hypoproteinemia without proteinuria and the lack of suggestive data of infective disease or anaphylaxis. The autopsy showed only findings of diffuse oedema with ascites and pericardial effusion, without evidence of infection or malignant disease, compatible with CLS.

**Conclusions:** RTX is currently considered to be an effective and safe treatment for NMO. Although the most frequent adverse events are postinfusion reactions and infections, the increasingly widespread and prolonged use of the drug could lead us to less known and potentially more serious adverse effects. Even this is the first CLS case in NMO patient treated with RTX, it is important to consider the diagnosis in any patient who presents sepsis syndrome, in particular, when no clear infectious process can be identified. Increased awareness of this problem will lead to a higher identification of cases and the better knowledge of monoclonal antibodies.

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 Jose Meca Lallana: nothing to disclose

## EP1789

### The national incidence of PML in Sweden, 1988 - 2013

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 Sweden*

**Background and aims:** An increase in the incidence of progressive multifocal leukoencephalopathy (PML) has been observed in MS patients in recent years. This study investigated the incidence of all PML diagnoses and patient characteristics in Sweden between 1988 and 2013.

**Methods:** All PML diagnoses in Sweden between 1988 and 2013 were identified in the National Patient Register. Information to validate the diagnosis and patient characteristics was obtained from medical records.

**Results:** Medical record review classified 108 out of 250 patients (43%) as definite (n=84), probable (n=4) or possible (n=20) PML according to diagnostic criteria. Accurate diagnoses were more common in records obtained from neurology departments (82% of patients who were assessed by neurology departments) compared with other departments (33%) ( $p < 0.001$ ). The incidence of PML increased from a largely stable level at 0.026 (95% CI: 0.021-0.031) per 100,000 individuals per year during 1988 - 2010 to 0.11 (0.083-0.137) during 2011- 2013 ( $p < 0.001$ ). Haematological malignancies (n=34), HIV/AIDS (n=33) and autoimmune disease (n=23) were the most common underlying diseases. Treatment with a monoclonal antibody prior to PML diagnosis was identified in 26 patients.

**Conclusion:** An increased incidence of PML in Sweden was observed and coincided with the prior use of monoclonal antibody treatment. The high level of misdiagnosis emphasises the importance of immediate contact with a neurology centre upon suspicion of PML.

## Disclosure

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## EP1790

### The therapeutic management of patients with multiple sclerosis in France: an analysis of the EGB database

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**Background and goals:** Around 100,000 people are currently diagnosed with Multiple Sclerosis (MS) in France. To date, available therapies for the disease do not cure MS and only prevent flares in the relapsing-remitting forms. The objective of the analysis was to describe the therapeutic management of patients with MS.

**Method:** The main French National Health Insurance database cover about 90% of the French population. Data from a random sample of  $\approx 600,000$  patients (1/97<sup>th</sup>) registered in this claim database were used to identify adults MS patients through their Long standing condition status (ICD-10 code: G35)/ hospital stays during the study period referencing MS as main diagnosis or related/ at least one reimbursement of an MS-specific drug over the 2007-2014 period. Treatment sequences were identified considering date of delivery of MS therapies in the database.

**Results:** A total of 940 patients were included in the prevalent MS population on January 1st, 2014. On average they were 50.9 ( $\pm 13.7$ ) years old. 71.4% of patients were female. Nearly all patients (91.7%) were visited at least once during the year by a GP and 38.9% a neurologist. Overall, 44.3% of patients have received at least one delivery of a primary therapy for MS in 2014 mostly beta-interferons and assimilated (28.8%), selective oral immunosuppressant (6.1%) non-selective oral immunosuppressant (5.7%), humanized monoclonal antibody anti-alpha-4 integrin (5.0%), oral Nrf2 pathway activator (3.1%), oral selective immunomodulatory (2.0%), chimeric anti-CD20 antibody (0.3%). 24.4% of patients had a symptomatic treatment at least once during the year (baclofen 17.7%) and 9.3% at least one delivery of injectable corticosteroids. A longitudinal analysis over 2007-2014 show most patients were treated discontinuously with rather long period of time without primary therapies for MS. In 2014, 22.1% of patients benefited of technical aids for their disabilities and 46.9% of patients had at least one physiotherapy session during the year. Finally, 6.2% of patients were hospitalized for MS for an average duration of 3.6 days.

**Conclusions:** Management strategies in MS were modified in the last decade with the marketing of disease-modifying treatments. However, in our sample, slightly more than half patients did not receive any primary therapies for MS while a significant part of

patients continue to experience symptoms and disabilities associated with MS.

### Disclosure

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### EP1791

#### Use of complementary and alternative medicine in Hispanic patients with multiple sclerosis

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**Introduction:** Multiple sclerosis (MS) is a complex disease with several symptomatic and disease modifying treatment options. As it is a disabling disease and none of these treatments warrants relief in all patients, some of them tend to resort to complementary and alternative medicines (CAM). CAM are those therapies that are not currently considered an integral part of conventional allopathic medical practice. They may lack biomedical explanations but as they become better researched. Different surveys in North America and Europe show a variable use of them, but there are not studies performed in neither Latin America nor Spain.

**Objective:** To set the frequency and describe the use of CAM use in a Hispanic population with MS.

**Methods:** An anonymous survey was performed in January 2017 in a Hispanic population with MS that participate in patient groups of the social network Facebook (closed groups *Esclerosis Múltiple* and *Amig@s con Esclerosis Múltiple*). Data obtained were age, sex, residence country, educational level, progressive or relapsing-remitting disease, current treatment, disability, and questions about use of CAM. A multivariate analysis was performed in order to identify predictors of use of CAM.

**Results:** 463 patients answered the survey. Average age was 41 (SD 9.73), Mean years of disease 9 (SD 7.4), 78% females. Most frequent residency countries were Spain, Mexico and Argentina. Relapsing - remitting had forms 59% and progressive forms 20%. Estimated disability showed 64% of fully ambulatory, 29% walked with assistance, and 7% restricted to wheelchair or bed. CAM were used in 51% of patients, of which 12% stopped immunomodulatory treatment to continue only with CAM, and 34% never told their doctor that they used CAM. Most frequent CAM were dietary supplements and acupuncture. 82% noted some benefit, most frequent symptomatic relief. 6% reported any adverse event related to CAM. Multivariate analysis identified as predictors of CAM use higher level of education  $p = 0.0008$ , OR 1.8 (CI 1.28 - 2.54); country of residence Venezuela  $p = 0.036$ , OR 1.26 (CI 1.01 - 1.56); and fully ambulatory 0.002, OR for restricted to bed 0.57 (CI 0.39 - 0.81).

**Discussion:** CAM utilization in this Hispanic sample seems to be significant, with an important number of patients stopping their

treatment or not consulting with their doctors. Treating physicians should be aware of this problem and discuss with their patients.

### Disclosure

No conflict of interest to declare.

### EP1792

#### A multi-centre observational analysis of persistence to treatment in the new MS era: the RESPECT study

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**Background:** In recent years there has been an increasing availability of disease-modifying treatments (DMTs) for relapsing-remitting multiple sclerosis (RRMS), including oral drugs. The common perception is that these oral drugs are more accepted and tolerated by patients than self-injectable DMTs. However, evidence that the route of administration has a relevant effect on persistence to treatment is not established yet.

**Objective:** To investigate the short-term persistence to treatment with self-injectable or oral DMTs in patients with RRMS.

**Methods:** We retrospectively collected data of patients attending 21 Italian MS Centres and one MS Centre in Wales, UK. Patients were considered eligible if they started a self-injectable or oral



DMT (excluding fingolimod) from January to December 2015. We estimated the proportion of patients discontinuing the treatment within a follow-up period of 12 months and analysed reasons for discontinuation. A Cox regression model (stratified by Centre) was run to explore baseline predictors of treatment discontinuation.

**Results:** We analyzed data of 1,841 consecutive patients (1,293 F, 548 M) with a mean age of 40 years and median EDSS of 2.0. Of them, 631 (34%) were treatment-naïve, while the remaining 1,210 (66%) were switched from another DMT. The most frequently prescribed treatment was dimethyl fumarate (n=1,050; 57%), followed by teriflunomide (n=174, 15%), glatiramer acetate (GA) 20 or 40 mg (n=175; 9.5%), low-frequency (LF) i.m. or s.c. pegylated Interferon beta (IFNB)-1a (n=174, 9.5%), high-frequency (HF) s.c. IFNB-1a or 1-b (n=165, 9%).

A total of 366 (20%) patients discontinued the prescribed DMT after a median time of 6 months due to lack of tolerance (n=166), disease activity (n=98), adverse event (n=62), pregnancy planning (n=22) or unspecified reasons (n=21).

The highest discontinuation rate was observed in patients treated with LF-IFNB ( $p < 0.02$  versus each other DMT). There was no significant difference in discontinuation rate between oral drugs and HF-IFNB or GA ( $p > 0.3$ ). Female sex (HR=1.45,  $p=0.003$ ) and previous exposure to  $>2$  DMTs (HR=1.66,  $p=0.009$ ) were other independent risk factors for treatment discontinuation.

**Discussion:** Poor tolerability was the most common cause of treatment discontinuation in the short-term period. Oral drugs did not show a better tolerability with respect to self-injectable DMTs. Persistence to treatment represents a clinical challenge, irrespective of the route of administration.

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## EP1793

### Tolerability and persistence in therapy with PEGylated-IFN: results from a multicentric observational study in Italy

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**Objectives:** PEGylated Interferon (PEG) pivotal trials in Multiple Sclerosis (MS) have shown its efficacy compared to placebo, with a favourable tolerability profile. Aim of this study is to confirm these data in a real-life setting, and understand predictors of good tolerability and persistence in therapy.

**Materials and methods:** We invited MS centres in Lombardy to collect data from all RR-MS patients receiving PEG, recording demographic and clinical features and laboratory tests results.

**Results:** 251 patients (166F) were enrolled from 10 MS centres (mean age  $42.1 \pm 10.6$  years (y)), mean disease duration  $11.2 \pm 7.8$  y). Mean ARR in the two y before PEG was  $0.2 \pm 0.2$ ; median baseline EDSS was 1.5. 31/251 patients were treatment naïve and 94/251 started PEG switching from Interferon (IFN) once a week (IFN-1w), 109/251 switched to PEG from IFN multiple times a week (IFN-mw), while 17/251 switched from other therapies. Mean follow up was  $11 \pm 3.3$  months (mo) (median 11 mo, I and III quartiles: 8-13 mo). 169/251 patients reported Adverse Events (AEs): 55% (n=139) complained of flu-like syndrome (FLS) (in 28 cases leading to PEG discontinuation), and 27% of skin reactions. FLS was reported more frequently by patients switching from IFN-1w (69%), compared to patients previously treated with IFN-mw (43%), naïve (58%) or other patients (53%) ( $p=0.03$ ). Other notable AE included blood test count abnormalities (7%, one leading to discontinuation) and elevation in transaminases (3%, one leading to discontinuation). 51/251 patients stopped PEG: 38 for AEs, 5 for pregnancy and 8 for disease activity. 29% of the patients switching from IFN-1w stopped PEG, with respect to patients previously treated with IFN-mw (14%), naïve (6%) or other patients (41%). Predictors of non-persistence in therapy were switching to PEG from IFN-1w (HR 0.15, 95% CI: 0.03-0.76,  $p = 0.02$ ), but not gender, age, disease duration, baseline EDSS or the number of previous therapies. Among patients switching to PEG from IFN-mw no increase in the relapse rate was observed.

**Discussion and conclusion:** Even with the limitations of an open label study with a short follow-up, our data seem to confirm the good tolerability profile of PEG. Switching from non-PEGylated IFN to PEG doesn't seem to affect relapse rate. Persistence in PEG is maximized in patients whose previous IFN regime was of high frequency, probably because the benefit of a sharp decrease in the number of injections overwhelms PEG side effects.

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VTC acted as an Advisory Board member of Novartis and Merck-Serono, received funding for traveling and honoraria for speaking or writing from Teva, Biogen, Genzyme, Merck-Serono and Almirall. She received support for research project by Almirall.

VM served on the scientific advisory board for Merck, Roche e Genzyme-Sanofi

CB served on the scientific advisory board for Merck

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MR, AMP, ES, LMF, LA, and ST have nothing to disclose

## EP1794

### Bridging the gap-challenges in switching from fingolimod to alemtuzumab

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**Background:** Switching between disease modifying treatments in Multiple Sclerosis (MS) is becoming increasingly complex. In patients failing Fingolimod therapy, treatment can be escalated to Alemtuzumab to achieve disease suppression. Potential difficulties with this treatment strategy include rebound disease activity, as there have been reports of treatment failure in up to 25% of patients who have switched from Fingolimod to Alemtuzumab. This process is thought to be mediated by prolonged sequestration of auto-reactive lymphocytes due to Fingolimod, which are then released following discontinuation. These cells (whilst sequestered) can also avoid the activity of Alemtuzumab, later causing ongoing disease activity despite Alemtuzumab treatment.

**Methods:** Patients with relapsing remitting MS who switched to Alemtuzumab from Fingolimod were reviewed from a South West Wales cohort.

## Results

Case 1: A 31-year old female with relapsing remitting MS was escalated to Alemtuzumab from Fingolimod due to clinical relapse activity. Following the first course of Alemtuzumab treatment she suffered 2 further relapses and her MRI demonstrated multiple new T2 lesions and 6 Gadolinium-enhancing lesions. Her second course of treatment has been successful, achieving current disease stability.

Case 2: A 43-year old female with relapsing remitting MS was escalated from Interferon beta to Fingolimod and had been stable for 3 years. She subsequently developed clinical and radiological disease activity and was switched to Alemtuzumab. In view of the risk of treatment failure, a 12-week washout period was instituted, with a pulse of Methylprednisolone at 8 weeks to reduce the chance of rebound disease. On cessation of Fingolimod, MRI disease activity was noted at 8 weeks and clinical disease activity at 12 weeks. The first course of Alemtuzumab however was successful with no clinical or radiological disease activity.

**Conclusion:** The complexity of managing MS patients with disease modifying treatments, and especially of managing the complications of switching between treatments is rapidly evolving. We present an example of treatment failure following escalation from Fingolimod to Alemtuzumab. We discuss a treatment strategy that includes an extended washout period with corticosteroid cover, to balance the risk of potential Alemtuzumab treatment failure against Fingolimod withdrawal rebound disease activity.

## Disclosure

M Hu: nothing to disclose.

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O R Pearson: served on the scientific advisory board for Biogen, Novartis, Roche, UK MS Register and has received travel funding and/or speaker honoraria from Biogen, Roche, Merck Serono, Novartis, Teva, Genzyme Sanofi.

## EP1795

**Neuromyelitis optica spectrum disorders: recurrence of relapses after suspension of immunosuppressive therapy in Venezuelan patients**

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**Background:** Neuromyelitis Optica Spectrum Disorders (NMOSD) is an autoimmune disease of the central nervous system considered rare in some countries. Due to the high risk for disability, maintenance therapy is required to avoid further attacks. In Venezuela the treatment is based on immunosuppressant drugs Azathioprine, Mycophenolate Mofetil and low oral dose of corticosteroids. Because other types of drugs like Rituximab, a monoclonal antibody is not provided by the Social Security for this disease. There has been an abrupt discontinuation in the availability of these drugs.

**Objectives:** To demonstrate that the interruption of the immunosuppressive drug maintenance treatment in NMOSD is related to increased risk of relapses.

**Methods:** A Retrospective study including 40 consecutive NMOSD patients was performed in Venezuela. Demographic, clinical, number of relapses, serological status, immunosuppressor treatment with Azathioprine and Mycophenolate Mofetil between April 2015 and April 2016 were analyzed.

**Results:** Of 40 female Venezuelan relapsing NMOSD patients, in maintenance treatment with Azathioprine and Mycophenolate Mofetil 42%(n=17) stopped or decreased the dose of the drugs: 94 %(n=16) of them had a stable disease with an annualized rate of 0.67 and only 6%(n=1) had aggressive course with this treatment, Azathioprine 64%(n=11) and Mycophenolate Mofetil 35%(n=6). From the patients that suspend the treatment 94% (n=16) had a relapse between 30 to 90 days.

**Conclusion:** It is recommended to maintain an effective dose of the immunosuppressive treatment with Azathioprine and Mycophenolate Mofetil in patients with relapsing NMOSD, in order to avoid relapses and progression.

**Disclosure**

nothing to disclose

## EP1796

**How neurologists approach the therapeutic choice in multiple sclerosis: preliminary results of an Italian survey**

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**Background:** Risk propensity, determined by contextual and personality factors, plays a role in the therapeutic choice of a person with multiple sclerosis (PwMS), due to difficulties in the perception and evaluation of benefit-risk ratio of available disease-modifying therapies (DMT). However, nothing is known about its possible role on physicians facing the choice of a DMT.

**Aim:** To evaluate risk propensity in a cohort of neurologists working with PwMS.

**Materials:** A questionnaire composed of:

- Socio-demographical/professional questions;
- Control Preferences Scale (CPS) adapted to physicians;
- Metacognitive Functions Screening Scale-30 (MFSS-30);
- Zuckerman-Kuhlman Personality Questionnaire (ZKPQ);
- Questions about levels of luck/depression/optimism before and after a potential MS diagnosis;
- Questions and decision trees about admissible levels of severe disability and death risks in response to different pharmacological profiles;
- Original CPS.

**Methods:** So far, sixty Italian physicians, previously contacted by mail, filled in the questionnaire, completing the 'a-d' section, considering their role of neurologist and the 'e-g' section, making the effort of being a potential PwMS.

**Results:** Subjects, aged between 26 and 65, had a mean MS experience (MSE) of 12.8±8.4 years and an experience of adverse events (EAE) of 77%. Two of them were eliminated from the e-g section analysis, due to potential metacognitive dysfunctions identified with MFSS-30. The included subjects declared they would feel significantly less fortunate, optimist and more depressed after an MS diagnosis. To gain 2 years of disease stability they would accept a therapy with a risk of severe disability and death of 2.3% and 1.0%, respectively; while they would accept up to 3.3% and 2.0%, to gain 4 years. MS progression is the risk which mainly worries 40% of neurologists, followed by PML (30%) and leukemia (23%). These results correlate only partially with ZKPQ impulsive sensation seeking, without relations with age, gender, MSE, EAE and professional experience. An active patient's role and a shared one were preferred, respectively, by 53% and 45% of the neurologists, with consistent results switching to the potential patient condition.

**Conclusions:** In Italian neurologists working with PwMS, risk propensity is mainly related to personality and not to contextual factors, suggesting the importance of the self-awareness, alongside with the professional knowledge, in approaching to therapeutic choice.

**Disclosure**

Eleonora Minacapelli received honoraria for consultancy and travel expenses from Italian Multiple Sclerosis Foundation (FISM) and Cesare Serono Foundation.

Monica Falautano and Francesca Sangalli declare no conflict of interests.

Giancarlo Comi has received compensation for consulting services and / or speaking activities from Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Roche, Almirall, Excemed, Celgene, Forward Pharma.

Vittorio Martinelli received honoraria for speaking and/or for consultancy and support for travel expenses and participation in Congresses from Bayer, Biogen-Idec, Merck-Serono, Novartis, Genzyme and Teva.

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## EP1797

**Factors influencing disease modifying therapy prescribing rates and practices: a qualitative study of neurologists and nurses**

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**Background:** The proportion of people with relapsing forms of multiple sclerosis prescribed disease modifying treatments (DMTs) in the United Kingdom is considered low compared with other countries. National surveys also indicate large differences between UK regions (England, Wales, Scotland, Northern Ireland) in the proportion of people eligible for DMTs who are prescribed these medications. Despite this, there has been little research into factors influencing prescribing which could explain variation in treatment rates, and very few studies of clinicians' views, decision-making processes, and prescribing practices. This study aims to investigate the experiences of neurologists who prescribe DMTs and MS specialist nurses who help patients access these drugs, to identify factors influencing prescribing and uptake of DMTs.

**Methods:** Semi-structured hour-long interviews were conducted with 18 consultant neurologists and 16 specialist nurses. Participants were purposively sampled from diverse National Health Service (NHS) settings across the four UK nations. Interview transcripts were analysed using a thematic framework analysis.

**Results:** Prescribing of DMTs is influenced by organisational, inter-professional, and individual factors. Services differed in procedures for identifying relapses, role of MS nurses in ascertaining eligibility for DMTs and facilitating patients' decisions, and responsibilities of general neurologists versus MS specialist neurologists. Individual prescribing practices are influenced by organisational prescribing "cultures", informal "benchmarking" within peer networks, and prior experience with different DMTs, though non-specialist clinicians prescribing in isolation may miss out on these influences. Prescribers differ in their perceptions of the benefits and risks of DMTs, their preferences for managing patient decision-making, and personal "thresholds" for discerning relapses and determining eligibility for DMTs according to treatment guidelines. These individual differences influence conversations with patients and the strength of treatment recommendations. Variation in practice was more evident between prescribing centres and between individual prescribers than between UK regions.

**Conclusions:** These findings reveal organisational and individual differences in DMT prescribing practices, which have implications for equitability of care for people with relapsing multiple sclerosis seeking disease modifying therapy.

**Disclosure**

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E. Cameron, G. McDonnell, and D. French have no conflicts of interest to declare.

D. Rog has served on advisory boards and/or received speaking fees from Biogen, Sanofi Genzyme, Merck, Roche, Novartis and Teva Pharmaceuticals, and has had research support to an institutionally-managed fund from: Biogen, GW Pharma, Sanofi Genzyme, Merck, Mitsubishi, Novartis and Teva Pharmaceuticals. J. Overell has received honoraria for speaking engagements and attendance at advisory boards from Teva, Novartis, Merck-Serono, Genzyme, Roche, Allergan and Biogen. Additionally his department has received educational grants, research funding and funds to provide nursing and administrative staff from these companies

O. Pearson served on the scientific advisory board for Biogen, Novartis, Roche, UK MS Register and has received travel funding and/or speaker honoraria from Biogen, Roche, Merck Serono, Novartis, Teva, Genzyme Sanofi.

## EP1798

**Natalizumab treatment is associated with improved patient-reported outcomes in the treatment of multiple sclerosis: results from a systematic literature review**

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**Background:** With over 10 years of post-marketing experience, natalizumab (NTZ) has well-established efficacy and long-term safety in relapsing-remitting multiple sclerosis patients. In addition to demonstrating the effectiveness of NTZ in significantly delaying and improving disability, clinical trials and real-world observational studies have shown significant improvement in patient-reported outcomes (PROs). These measures complement clinician-reported data and provide data on treatment impact from the patient perspective.

**Objectives:** To identify, synthesize, and summarise available PRO data for multiple sclerosis (MS) patients treated with NTZ.

**Methods:** A systematic search of the peer-reviewed Embase, Medline, and Cochrane databases (January 2006-April 2017), and conference proceedings (2015, 2016), was performed. Selection of eligible studies, data extraction, and quality assessment were undertaken independently by 2 researchers. Selection criteria included studies of NTZ-treated adults with MS that reported on any PRO outcome.

**Results:** Thirty-seven publications were identified, which included sample sizes ranging from 9 - 2,822 participants. The most frequently assessed domains included mental/psychosocial (16 studies), fatigue (16 studies), physical functioning (15 studies), depression (14 studies) and overall health-related quality of life (HRQoL) (9 studies). The most frequently used PROs included the MS Impact Scale (7 studies), Beck Depression Inventory (7 studies), Fatigue Scale for Motor and Cognitive Functions (6 studies) and Fatigue Severity Scale (6 studies). Changes in PRO scores were primarily examined over 6 months

to 5 years. NTZ generally improved HRQoL, physical functioning, cognition, depression, work productivity, bladder function and fatigue as compared to baseline scores. Eleven studies presented results comparing NTZ-treated patients to those being treated with other disease-modifying agents (DMTs), primarily interferon and fingolimod. The majority of these comparative studies favoured NTZ over other DMTs in the assessed domains.

**Conclusion:** Over the last 10 years, NTZ has demonstrated an improvement in PROs in most major domains of physical, emotional and symptom assessment. The analysis of these relevant PROs will help enable more informed health care decision-making beyond the traditional clinical endpoints.

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## EP1799

**REALMS study: a non-interventional retrospective, multicenter study to evaluate the effectiveness of fingolimod therapy in real-life clinical practice in patients with relapsing-remitting multiple sclerosis (RRMS) in Portugal**

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**Background:** Fingolimod is a sphingosine 1-phosphate receptor (S1PR) modulator, approved for the treatment of RRMS in over 80 countries, including Portugal since March 2012. The increasing experience with fingolimod allows the collection of local

real-world evidence (RWE) data to evaluate fingolimod's clinical impact in the local setting.

**Objective:** To collect retrospective RWE from the clinical records of RRMS patients concerning the efficacy of fingolimod treatment.

**Methods:** 275 patients with RRMS from 9 centers across Portugal. The neurologists from the participant sites have reviewed all the clinical histories from patients being treated with fingolimod for at least 12 months.

**Results:** The median (IQR) age of the patients was 41.0 (12.0 years), ranging from 18 to 78 years. When analyzed as percentage, relapse-free patients increased steadily and significantly up to the 3rd year after switching to fingolimod. The percentage of patients free from relapses increased significantly over the years after fingolimod treatment when compared to the previous year, reaching 91% after 3 years compared to 45%, one year prior to starting fingolimod treatment. Regarding EDSS, these patients remain stable over the 3 years.

**Conclusions:** The results from the REALMS study support the clinical efficacy of fingolimod that is demonstrated in phase III clinical trials and with real-world evidence data.

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## EP1800

**Bicycle ergometry does not improve verbal memory in mild relapsing remitting MS - results of a RCT**

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**Background:** Research in ageing and early dementia indicates a potentially protective effect of aerobic training on cognition. However, very few exercise intervention studies have been performed in MS focusing cognitive functioning. A previous pilot

study in progressive MS has shown improved verbal learning and delayed recall as well as improvements in other cognitive and neuropsychiatric symptoms.

**Objective and methods:** This study aimed to confirm beneficial effects of exercise on cognition in a randomized waitlist control study of relapsing-remitting MS patients. The primary outcome was verbal memory (Verbal learning and memory test, VLMT, learning and recall condition). Secondary outcomes were VO<sub>2</sub>peak and VO<sub>2</sub>peak/kg as well as 7 other cognitive measures of attention, information processing and visuospatial memory. Patients were randomized to 12-week training or a waitlist control group. Patients in the training group exercised according to an individually tailored training plan (based on cardiorespiratory fitness by ramp ergometry at baseline, t<sub>0</sub>). The training was aimed at 2-3 sessions per week until week 12 (t<sub>1</sub>), with a follow-up at week 24 (t<sub>2</sub>). ANCOVA analysis was performed controlling for baseline scores based on the intention-to-treat dataset and missing data imputed by last-observation-carried-forward (LOCF).

**Results:** From 77 screened RRMS patients 57 patients (69% female, mean age 39 years, mean disease duration 5.7 years, median EDSS 1.5) (CG n=27; IG n=30) completed the core study (t<sub>0</sub>-t<sub>1</sub>). All IG patients performed training intervention, however only 22 outnumbered 18 training sessions. Median number of training session was 22. While in general cognitive impairment was low, VLMT scores were not improved through the intervention. Work load increased during the training but only VO<sub>2</sub>peak/kg was significantly induced in the IG from t<sub>0</sub>-t<sub>2</sub> (time by group interaction F=3.307; p=.045).

**Conclusion:** This study could not confirm previous data on improving verbal learning and delayed recall through an exercise intervention. A possible explanation is that the cohort was only mildly disabled and without substantial cognitive impairment at baseline. Similar to aging individuals the impact of exercise on different cognitive domains might differ based on MS disease stage. Per protocol data analysis and other secondary outcome measure analysis is ongoing.

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## EP1801

### Treatment patterns of disease modifying therapies in MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions)

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**Background:** Use of disease modifying therapy in real-world MS populations is heterogeneous, reflecting physician and patient preferences, and health system considerations. For example, in the single-centre EPIC cohort, 40.4% of patients were not on a disease modifying therapy (DMT) at baseline, while in MSBase, an international multi-centre cohort, 21.9% of patients were not on a DMT. Variability in DMT use across practices, regions, and countries has received little systematic study to date. Important confounders or biases (i.e. channelling bias) may underlie this variability and should be taken into account conducting observational patient outcomes research.

**Objectives:** To describe treatment patterns and associated demographic and clinical characteristics among patients participating in the MS PATHS network.

**Methods:** During routine clinic visits patients answered standardized questionnaires, including use of DMTs, using the MS Performance Test, an iPad-based device. Current DMT use, patient demographics, and MS characteristics were characterized and analyzed using descriptive statistics, ANOVA, and Chi-square tests of independence.

**Results:** The sample comprised 1353 patients. Mean (SD) age was 48.9 (12.0), disease duration 12.2 years (9.4), age of diagnosis was 36.4 (10.9) and PDDS was 2.4 (2.2). 19.2% of patients reported no current DMT use. This group was older and more disabled compared to the 80.2% of patients who reported current DMT use. The five most common DMTs (in descending order) were dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab and interferons. In comparison, the five most common DMTs based on US market estimates were glatiramer acetate, interferons, dimethyl fumarate, fingolimod and natalizumab. Within MS PATHS the longest disease duration (mean=17.5 years, sd=10.5) and the lowest PDDS scores (1.5, 2.0) were among interferon patients; the youngest age (42.0, 10.2) was observed among natalizumab patients.

**Conclusions:** DMT use patterns differed in the MS PATHS network sites compared with external benchmarks. Overall DMT use was similar to MSBase, but higher than reported from EPIC. Glatiramer acetate and interferon use was less frequent in MS PATHS sites compared to US market estimates. MS PATHS interferon users had longer disease duration and lower disability scores. Factors relating to treatment pattern heterogeneity across the international network will be presented.

## Disclosure

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Megan Hyland is employed by the University of Rochester which receives funding from Biogen, Chugai and Novartis.

## EP1802

### The effect of pilates training and massage therapy on plasma serum levels of IL-17 and IFN $\beta$ as pro-inflammatory cytokines in patients with multiple sclerosis (MS)

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**Background:** Multiple Sclerosis (MS) is a chronic, debilitating nervous system disease, which damages the myelin of the central nervous system. The most common symptoms include fatigue, muscle spasms, tremors, double vision, lack of balance, and impaired walking. Cytokines play an important role in the pathogenesis of the disease and are considered an important objective for therapeutic intervention. IL<sub>17</sub> has a direct relationship with MS. On the other hand, IFN $\beta$  plays a key role in MS improvement. This article aimed to study The effect of Pilates training and massage therapy on plasma serum levels of IL<sub>17</sub> and IFN $\beta$  as pro-inflammatory cytokines in patients with multiple sclerosis (MS).

**Methods:** This is a clinical trial. A total of 36 women- who had medical file in Multiple Sclerosis society of Tabriz, Iran - were enrolled as the sample. The degree of the disease was between 0 and 4/5. The average length of disease was 2 $\pm$ 7 and the patients were between 30 and 40 years old. Selected and split in to 4 groups. Massage (n=9), pilates (n=9), pilates + massage (n=9), and a control (n=9). they were randomly assigned to Pilates and Massage groups. Exercise lasted for 8 weeks, 3 times a week. Each session lasted 40- 60 minutes: 20-40 minutes for Pilates and 20 -30 minutes for massage. Blood samples were taken before and after intervention and massage in order to measure the blood variables. Serum levels of IL<sub>17</sub> cytokine and IFN $\beta$  were measured using the ELISA. The data were analyzed by correlated t-test and ANOVA using spss20. The significance level was considered.(p< 0/05).

**Results:** Showed that 8 weeks of Pilates and Massage caused a significant decline in IL<sub>17</sub> in Pilates, Massage, and Pilates + Massage groups. IFN $\beta$  also increase in Massage and Massage + Pilates groups. (P< 0/05).

**Conclusion:** Since Pilates coupled with Massage reduced pro-inflammatory IL<sub>17</sub> cytokine and increase IFN $\beta$  of MS patients, it seems that Pilates and Massage can be used as a complementary treatment along with other drug therapies for preventing the progress of MS.

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## EP1803

### Early MRI findings during disease rebound in a natalizumab-treated MS patient and follow-up during transition to alemtuzumab

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**Background and goal:** To report early MRI findings in a clinically unstable patient with active MS following natalizumab cessation and during alemtuzumab initiation.

**Methods:** Patient case report.

**Results:** The patient (female, aged 39) had a 21-year history of MS, including periventricular T2 lesions, multiple T1 lesions, and signs of brain tissue loss. Prior MS treatments included SC and IM IFNB-1a, SC IFNB-1b, glatiramer acetate, fingolimod, and 2 separate periods of natalizumab (total: 75 cycles; discontinued due to disease activity and John Cunningham virus [JCV] antibody positivity). Three months after natalizumab cessation, the patient was hospitalised with severe relapse (dysarthria, diplopia, right hemiparesis); MRI showed a new, non-Gd-enhancing left midbrain lesion. Methylprednisolone and IVIG were administered. Two weeks later, the patient was confused, unable to walk, and LP showed red blood cells (RBC) 2/ $\mu$ L, white blood cells (WBC) 13/ $\mu$ L, protein 39 mg/dL, glucose 52 mg/dL, oligoclonal band-positive, and JCV PCR-negative (ARUP Laboratories). One week before alemtuzumab initiation, right hemiparesis had worsened; patient was lethargic and nonambulatory. Alemtuzumab Course 1

(12 mg; 5 consecutive days) was started 4.5 months after natalizumab cessation. On alemtuzumab

Day 3, decreased mentation, lethargy, poorly reactive left pupil, severe dysarthria, and right hemiparesis were noted. MRI after alemtuzumab Day 5 showed prominent diffuse T2 signals in juxtacortical regions of left temporal, parietal and occipital lobes, and right cerebellum. These lesions were not Gd-enhancing and were evident on diffusion-weighted imaging. Progressive multifocal leukoencephalopathy (PML) was considered; repeat CSF 10 days later demonstrated: RBC 14/ $\mu$ L, WBC 0/ $\mu$ L, protein 47 mg/dL, glucose 68 mg/dL, JCV PCR-negative (Quest Diagnostics). MRI 3 months post-alemtuzumab showed substantial resolution of previous diffuse T2 changes. At last follow-up 5.5 months post-alemtuzumab, clinical signs were improved with minimal dysarthria, mild right hemiparesis, and unassisted walking.

**Conclusion:** The basis of this patient's distinct MRI after discontinuing natalizumab is uncertain. Subsequent clinical and radiological improvement after alemtuzumab initiation indicates an explanation other than PML. This isolated case may suggest a beneficial role for alemtuzumab in a clinically unstable patient after natalizumab cessation, where a return of MS activity is occasionally observed.

**Study support:** None.

## Disclosure

**JLG:** Promotional speaker (Biogen, Mallinckrodt, Novartis, Sanofi Genzyme, and Teva); advisory board participant (Biogen, Genentech, Mallinckrodt, Novartis, Sanofi Genzyme, Serono, and Teva); clinical investigator (Biogen, Genentech, Novartis, and Sanofi Genzyme).

**DMZ:** Clinical investigator (Biogen, Genentech, Novartis, and Sanofi Genzyme).

**NAB:** Advisory board participant and consultant (Novocure, Inc).

**AKJ, CER:** Employees of Sanofi.

**DP:** Advisory board participant (EMD Serono, Novartis, Roche, Sanofi Genzyme, TG Therapeutics, and Vertex); grant/research support (Biogen).

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## EP1804

**Success of a CME-certified patient-physician video vignette in improving knowledge of clinical factors for the personalization of treatment selection in ms among neurologists**T. Finnegan<sup>1</sup>, G. Dolson<sup>2</sup>, S. Krieger<sup>3</sup><sup>1</sup>Medscape Education, Medscape, LLC, Glenside, PA,<sup>2</sup>Medscape Education, Medscape, LLC, <sup>3</sup>Icahn School of Medicine at Mount Sinai, New York, NY, United States

**Introduction:** Clinicians who care for patients with multiple sclerosis (MS) are in need of education that shows the clinical implementation of best practices for optimizing the personalization of treatment using available pharmacologic options. The goal of this study was to measure the effectiveness of an interactive, continuing medical education (CME)-certified, online, case-based video vignette with integrated expert perspectives to improve the knowledge of neurologists regarding clinical factors that impact treatment selection in MS.

**Methods:** The activity consisted of a single patient-physician video vignette that included 4 interactivity questions and expert faculty guidance on the elements of the case. The study design compared each participant's responses to questions posed before exposure to educational content (pre-assessment measurement) with the same participants' responses to the same questions after exposure to the educational content (post-assessment measurement). McNemar's chi-square test assessed differences from pre- to post-assessment. Cramer's V determined the effect size. The activity launched online on December 14, 2016, and data were collected through March 5, 2017.

**Results:** Comparison of answers before and after exposure to the educational activity demonstrated significant improvements in evidence-based decision making, with a medium educational effect size ( $n=77$ ;  $V=0.24$ ;  $P<.001$ ). As a result of participation, significant overall improvements were observed in several specific areas, including knowledge of the John Cunningham (JC)-virus index value that corresponds to the 2-year risk of PML in patients receiving natalizumab (174% relative improvement;  $P<.05$ ), identification of the safest disease modifying therapy (DMT) for pregnancy based on the ability to cross the placenta (17% relative improvement;  $P<.05$ ), and the appropriate use of high-dose steroids to treat an acute relapse during pregnancy (35% relative improvement;  $P<.05$ ). Participation in the activity resulted in a 22% improvement in confidence among neurologists in identifying when to switch DMTs in a patient with MS.

**Conclusion:** The CME intervention was successful in improving participating neurologists' knowledge and confidence in their ability to make evidence based, personalized treatment decisions for patients with MS. Subsequent education should address the practical application of the JC virus index.

**Disclosure**

Thomas F Finnegan: Nothing to disclose

Gena Dolson: Nothing to disclose

Stephen Krieger served as an advisor or consultant for: Acorda Therapeutics; Bayer HealthCare Pharmaceuticals; Biogen; Genentech, Inc.; Genzyme Corporation; Mallinckrodt; Novartis Pharmaceuticals Corporation; Teva Neuroscience, Inc.

## EP1805

**Patient reported adherence and treatment satisfaction in irish relapsing remitting multiple sclerosis patients treated with fingolimod**

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Novartis Pharmaceuticals, Dublin, Ireland

**Objective:** To assess the compliance and satisfaction in Irish patients taking fingolimod or relapsing-remitting multiple sclerosis (RRMS).

**Background:** Eleven disease modifying treatments are available in Ireland for the treatment of RRMS. Switching from one disease modifying therapy (DMT) to another is common in order to optimise treatment.

**Methods:** The Irish Fingolimod Nurse Service was launched in Ireland in July 2012. It offers first dose observation, patient education using motivational interviewing, blood and ophthalmology monitoring reminders and a free-phone helpline. Data was collected via a postal survey that was sent to 400 patients who signed up to the Nurse Service and who agreed to be contacted for follow-up. 167 patients returned a completed survey.

**Results:** 73.1% ( $n=122$ ) of respondents were previously treated with another DMT, with 25.1% receiving fingolimod as their first treatment. In patients who were treatment naïve, the average time from diagnosis to initiation of fingolimod was 2.5 years (range: 1-16 years), in patients who were previously treated with another DMT, the average time from diagnosis was 8.8 years (range: 1-41 years) Respondents switching to fingolimod from another DMT, mostly switched from an injectable DMT (iDMT) (76.2%), 10.7% switched from natalizumab and 9.8% switched from an oral DMT (teriflunomide or dimethyl fumarate). Lack of efficacy was reported as the most common reason for switching (60%). Respondents were treated with fingolimod for an average of  $16.8 \pm 10.9$  months. On a 100 point scale, patients who switched from a previous DMT scored their treatment satisfaction with fingolimod at an average of 87.5, while scoring their previous treatment, 45.8. Respondents who were treatment naïve scored their satisfaction at 86.4. 92.1% of patients reported that they remember to take their fingolimod tablet every day. The 7.9% who reported forgetting to take their treatment, missed 1.3 tablets per month on average.

**Conclusion:** Fingolimod is an option for RRMS patients switching drug modifying therapy with high patient satisfaction and significant rates of adherence.

**Disclosure**

Niamh Murphy is an employee of Novartis

Ruth MacIver is an employee of Novartis

Emma Horgan is an employee of Novartis

Kate Tyaransen is an employee of Novartis

## EP1806

**Comparison of injection site reactions and flu-like symptoms between users of peginterferon beta-1a and subcutaneous interferon beta-1a among persons with multiple sclerosis in the New York State Multiple Sclerosis Consortium**C. Vaughn<sup>1,2,3</sup>, K. Kavak<sup>1,3</sup>, A. Bushra<sup>3</sup>, M. Nadeem<sup>3</sup>, K.Zakalik<sup>1,3</sup>, B. Teter<sup>1</sup>, B. Weinstock-Guttman<sup>1,2,3</sup><sup>1</sup>New York State Multiple Sclerosis Consortium, <sup>2</sup>Neurology,

State University of New York at Buffalo, <sup>3</sup>Jacobs MS Center for Treatment and Research, Buffalo, NY, United States

**Background:** Interferon beta-1a is one of the most commonly prescribed disease modifying therapies (DMTs) to treat persons with multiple sclerosis (pwMS). However, use of these products is often accompanied by systemic symptoms and/or reactions. Comparing the tolerability of these medications in pwMS will provide valuable information to help clinicians and patients be better informed when considering specific therapeutic interventions.

**Objective:** Our objective was to evaluate and compare the presence of injection site reactions (ISR) and flu-like symptoms (FLS) between users of peginterferon beta-1a (PegIFN beta-1a) and subcutaneous (sq) interferon beta-1a tiw (SQ IFN beta-1a tiw).

**Methods:** Patients were part of the Tolerability study; an ancillary study of the New York State Multiple Sclerosis Consortium (NYSMSC). Of the 87 patients who have provided data to date, 50 (57.5%) used PegIFN beta-1a; while 37 (42.5%) used SQ IFN beta-1a tiw. Frequencies of FLS and ISR were calculated and compared between the PegIFN beta-1a users and SQ IFN beta-1a tiw group using Chi-square analysis. Furthermore, the severity of FLS and ISR were compared using a Mann-Whitney U test.

**Results:** There were no significant group differences with respect to age (mean overall=50.4 years, SD=12.1), sex (female n=61, 70.1%), disease duration (median= 12.4 years) or EDSS scores at baseline (median=3.0). FLS were reported in 33 (66.0%) PegIFN beta-1a users and 20 (54.1%) patients using SQ IFN beta-1a tiw (p=not significant [NS]). Median duration of FLS in the PegIFN beta-1a group was slightly longer than in the SQ IFN beta-1a tiw group (13-18 hours versus 0-6 respectively, p-value=0.004). ISRs were reported in the majority of patients in this study (46 [93.9%] in the PegIFN beta-1a group, 31 [83.8%] in the SQ IFN beta-1a tiw, p= NS). ISR redness was more frequently reported among patients using PegIFN beta-1a than interferon beta-1a users (46 [95.8%] vs 28 [75.7%] respectively, p=.006). Additionally, the severity of redness was more severe among PegIFN beta-1a users (median=3.0 vs 2.0, [0-5 scale], p< .001). There were no other group differences in reported symptoms or severity of symptoms.

**Conclusions:** On the whole, ISR and FLS are common among users of both types of IFN products. However, ISR redness was more frequently reported among PegIFN beta-1a users and duration of FLS was slightly longer in this group as well compared to users of SQ IFN beta-1a tiw.

## Disclosure

This study was sponsored by EMD Serono, Inc., Rockland, MA. Caila B Vaughn has nothing to disclose.

Katelyn S Kavak has nothing to disclose.

Aisha Bushra has nothing to disclose.

Muhammad Nadeem has nothing to disclose.

Karen Zakalik has nothing to disclose.

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Idec, Teva Pharmaceuticals, EMD Serono, Genzyme, Sanofi, Novartis and Acorda Therapeutics.

## EP1807

### BetaEval Global: prospective, non-interventional, multinational, observational cohort study of patients using BETACONNECT

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**Introduction:** BETACONNECT™ is an electronic autoinjector with communication capabilities that may help patients to remain adherent to interferon beta-1b.

**Methods:** Adherence (defined as completing ≥80% of prescribed injections) was assessed via autoinjector recordings over 24 weeks with visits at baseline, week 4, week 12 and week 24 in patients with relapsing-remitting MS (RRMS) or clinically isolated syndrome (CIS) who were treated with interferon beta-1b using BETACONNECT.

**Results:** 500 patients were enrolled with 498 in the full analysis set (median age: 44 years; 64.6% female, 28.8% completed college or university education). 474 patients (94.8%) were diagnosed with RRMS and 26 (5.2%) were diagnosed with CIS, with a median disease duration of 76.1 and 22.7 months, respectively. Median baseline EDSS score was 1.5 (N=449). Median adherence remained stable between 93.9% and 95.4% at all visits. 76.4%, 67.6%, and 81.1% of patients with non-missing data had ≥80% of planned injections recorded for study visits 1, 2, and 3, respectively. Multivariate logistic regression models indicated that higher adherence was associated with male gender, existing concomitant disease, shorter disease duration, higher SDMT score and higher satisfaction with the myBETAapp. 81.4% completed the study. The main reasons for study discontinuation were: switching to another injection method (25.8%), withdrawal of consent (22.6%) and becoming lost to follow up (17.2%). 83.4% of the patients still used BETACONNECT at their final visit.

**Discussion:** BetaEval Global showed a relatively high rate of adherence among patients with RRMS or CIS using BETACONNECT to administer interferon beta-1b. Additional research will explore device satisfaction and outcomes in patients using the autoinjector.

## Disclosure

This study was supported by Bayer AG.

F Patti served as an advisor for Almirall, Bayer, Biogen, Merck, Novartis, Sanofi Genzyme and TEVA and received grants for speaking activities from the same companies.

M Martínez-Ginés has received compensation for her contribution to the BetaEval Global study to the account of the Department of Neurology, Hospital General Universitario Gregorio Marañón-Madrid, by Bayer.

C Norenberg is a salaried employee of Bayer AG.

F Duarte Caron is a salaried employee of Bayer Healthcare.



**EP1808****Validation of the English translation of the Swedish symptom frequency intensity and distress (SFID) scale in persons with multiple sclerosis (PwMS) on interferon beta therapy**C.S. Casserly<sup>1</sup>, D. Bowman<sup>1</sup>, K. Gottberg<sup>2</sup>, A. Gardulf<sup>3</sup>, M. Heisel<sup>4</sup>, S.A. Morrow<sup>1</sup><sup>1</sup>Department of Clinical Neurological Sciences, Western University, London, ON, Canada, <sup>2</sup>Department of Neurobiology, Care Sciences and Society, <sup>3</sup>Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden, <sup>4</sup>Department of Psychiatry, Department of Epidemiology and Biostatistics, Western University, London, ON, Canada

**Introduction:** Interferon beta therapy has been a mainstay in the treatment of persons with multiple sclerosis (PwMS) since the introduction of the first MS disease modifying therapy, Interferon beta 1b<sup>1</sup> in 1993. However, a major limitation of these medications is their flu-like side effects (FLS). This necessitates assessment and monitoring of FLS in an attempt to maximize compliance.

**Background:** Major clinical trials<sup>2-6</sup> have reported on FLS, but the frequency, severity and duration of FLS have not been well characterized. Gottberg et al. addressed this question using the Swedish Symptom Frequency, Intensity and Distress (SFID) scale to evaluate patients' perceptions of the FLS experienced on interferon therapy<sup>7</sup>.

**Objective:** To validate the English SFID scale in a population of PwMS starting interferon therapies, as compared to a group of PwMS starting glatiramer acetate.

**Methods:** Sixty PwMS were recruited from the London (Ontario, Canada) MS clinic; 26 starting on interferon beta (any type) vs. 34 controls starting on glatiramer acetate. Interferon and glatiramer groups were similar in terms of age, sex, EDSS and disease duration at baseline; all had relapsing remitting MS, were relatively young (mean age 35.8 vs. 33.1), with a low EDSS (median 1.5 range 0-6 vs. median 1.5 range 0-4). Participants completed the SFID, Hospital Anxiety and Depression Scale (HADS), Fatigue Severity Scale (FSS), Pain Effects Scale (PES), Beck Depression Inventory, Fast Screen (BDIFS), Satisfaction with Life Scale (SWLS), Short Form Survey (SF-12), Health-100 and Symbol Digit Modality Test (SDMT) at weeks 1-8, monthly to 6 months.

**Results:** SFID total scores demonstrated significant positive associations with measures of fatigue and depression, demonstrating convergent validity. In contrast, there was no association between SFID scores and age, level of education and SDMT score, demonstrating discriminant validity. Scores on the SFID were significantly different between the interferon and glatiramer groups, and peaked in the interferon group at week 4, returning to baseline by month 6. The SFID scale had good internal consistency, significant test-retest reliability, and could discriminate between participants receiving interferon vs. glatiramer.

**Conclusions:** The SFID is a potentially valuable tool for the evaluation of FLS in PwMS on interferon therapy, providing improved quantification of FLS, and their impact on quality of life.

**Disclosure**

Courtney Casserly has received personal compensation for consulting for EMD Serono, Genzyme, Roche and received a travel grant from EMD Serono and Novartis, and received funding for

her Clinical Fellowship from Biogen Idec, and is a co-investigator on clinical trials for Genzyme and Roche.

In the last two years, Dr. Morrow has received honoraria for speaking, consulting, and advisory board participation from Biogen Idec, EMD Serono, Genzyme, Novartis, and Roche. She has acted as site principal investigator for clinical trials for Novartis, Genzyme and Roche. She has received investigator initiated trial funding from Genzyme.

Denise Bowman: nothing to disclose

Marnin Heisel: nothing to disclose

Kristina Gotberg: nothing to disclose

Ann Gardulf: nothing to disclose

**EP1809****Efficacy and treatment satisfaction after switching therapy in patients with relapsing-remitting multiple sclerosis: the multicentre, observational SURFINIA study**R. Mantegazza<sup>1</sup>, M. Olivelli<sup>2</sup>, S. Cottone<sup>3</sup>, V. Torri Clerici<sup>1</sup>, M.T. Ferrò<sup>4</sup>, D. De Pascalis<sup>5</sup>, A. Veneziano<sup>6</sup>, D. Cuomo<sup>6</sup><sup>1</sup>Istituto Nazionale Neurologico Carlo Besta, Milan, <sup>2</sup>Azienda Ospedaliera Universitaria Senese, Siena, <sup>3</sup>Ospedali Riuniti Villa Sofia-Cervello, Palermo, <sup>4</sup>Azienda Socio-Sanitaria Territoriale di Crema, Crema, <sup>5</sup>Ospedale Sant'Eugenio, Roma, <sup>6</sup>Teva Italy, Milan, Italy

Although disease modifying therapies (DMTs) are effective in patients with relapsing-remitting multiple sclerosis (RRMS), some patients may require switching to another DMT due to sub-optimal efficacy and/or intolerable toxicity. This multicentre, observational study aimed to assess the clinical course of patients with RRMS who switched DMT for these reasons in a real-life clinical setting in Italy.

Adult patients with confirmed RRMS receiving first-line therapy with a DMT who were candidates for switching according to their treating physician were enrolled and followed for 1 year. The primary endpoint was the annualized relapse rate (ARR); secondary endpoints included the proportion of relapse-free patients, time to first relapse, and patient-reported treatment satisfaction (using the Treatment Satisfaction Questionnaire for Medication [TSQM-9]). Safety was assessed by recording adverse events (AEs).

A total of 150 patients were enrolled (mean age 40.2 years; 28% male). Compared with the mean ARR at 2 and 1 years before switching ( $0.60 \pm 0.57$  and  $0.78 \pm 0.77$ ), post-switch ARR was significantly decreased ( $0.28 \pm 0.80$ ;  $p < 0.0001$ ). Patients switching because of treatment failure had greater mean ARR decreases versus those switching for other reasons when compared with baseline at 2 years ( $-0.44 \pm 0.85$  vs  $-0.24 \pm 0.91$ ;  $p = 0.04$ ) and 1 year ( $-0.77 \pm 1.03$  vs  $-0.30 \pm 0.96$ ;  $p = 0.0004$ ) before switching. Relapse-free rates were 42% at 1 year before switching and 86% post switch ( $p = 0.0001$ ). Time to first relapse after switching therapy did not differ between patients who switched DMT due to treatment failure versus other reasons. Patients had significant improvements from baseline to 12 months in TSQM-9 effectiveness and global satisfaction scores ( $-11.47$  and  $-11.69$ ;  $p < 0.0001$ ); there was no difference in treatment satisfaction between those switching because of treatment failure versus other reasons. AEs were reported in 47.3% of patients, while 4.0% of patients reported serious AEs. The most

common AEs reported were multiple sclerosis relapse (16.0%), influenza-like illness (8.0%) and increased transaminases (3.3%). Thirty-nine patients reported 68 treatment-related AEs, which were mostly injection-site reactions.

These results show that switching from first-line DMT therapy to another DMT improves relapse rates in patients with RRMS without notable safety concerns, particularly in patients who switched DMT therapy because of therapy failure rather than other reasons.

## Disclosure

Dario Cuomo and Antonella Veneziano are employees of Teva Italia.

The other Authors declare no competing interests.

## EP1810

### Knee flexor muscle strength is related to gait performance in women with multiple sclerosis but not for healthy women

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**Background:** Motor impairment in people with Multiple Sclerosis (MS) may result in reduced mobility and physical activity level, which can culminate in further disabilities. Changes in balance control, loss of muscle strength and gait disorders are frequent in MS patients. The measurement of these parameters are important in turn to change the way to manage exercise programs for people with MS.

**Objectives:** The purpose of this study is to compare knee muscles strength between women with MS and controls without MS. In addition, to investigate the correlation between muscle strength, balance and gait parameters in our sample.

**Methods:** 15 women with relapsing-remitting MS, EDSS (1-3), age=29.2(±4) y, weight=59.5(±10) kg and height=161.4(±5) cm. The control group was composed of 11 paired women without MS, age=29.1(±5.7) y, weight=60(±10.5) kg and height=161.5(±5.1) cm. The peak torque was measured by isokinetic dynamometry (Biodex System 3) in four trials for each angular speed (60°.s<sup>-1</sup>, 90°.s<sup>-1</sup> and 180°.s<sup>-1</sup>), for both legs. The balance control was evaluated with a force platform (AMTI Inc) on upright position using a foam. The 6 minute walk test was performed and total distance was calculated.

**Results:** Regarding knee muscles strength, MS women did not differ from control group. The correlation between muscle strength and balance was not significant. The control group showed strong correlation ( $p < 0.05$ ) between distance and knee extensors (KE) strength, for all angular speeds: 60°.s<sup>-1</sup>( $r=0.87$ ), 90°.s<sup>-1</sup>( $r=0.84$ ), 180°.s<sup>-1</sup>( $r=0.82$ ). For the MS group, not only KE strength revealed correlation with distance, 60°.s<sup>-1</sup>( $r=0.84$ ), 90°.s<sup>-1</sup>( $r=0.87$ ), 180°.s<sup>-1</sup>( $r=0.84$ ), but also the knee flexors (KF) muscles, 60°.s<sup>-1</sup>( $r=0.86$ ), 90°.s<sup>-1</sup>( $r=0.80$ ), 180°.s<sup>-1</sup>( $r=0.80$ ).

**Discussion and conclusions:** The literature report that KE strength is best related to walking speed in healthy subjects. However, MS patients KF strength is most strongly related to gait velocity and distance. The results of this study agree with the recent findings, suggesting that people with MS seems to be more dependent on KF muscle to walk. Our results suggest that rehabilitation protocols for MS patients must include strength training programs which should prioritize strengthening of the KF and KE muscles.

## Disclosure

Cintia Ramari: nothing to disclose.

Andrea G. Moraes: nothing to disclose.

Carlos B. Tauil: nothing to disclose.

Ana C. de David: nothing to disclose.

## Treatment of specific symptoms

## EP1811

### Therapeutic benefit of uncobotulinum toxin A for the spasticity of the triceps surae in patients with multiple sclerosis: an observational study on gait spatiotemporal parameters

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**Introduction:** Few data are available on the use of botulinum toxin for spasticity treatment in multiple sclerosis (MS). In a previous study we found that one of the main therapeutic goals was the improvement of walking, in patients suffering from spasticity of the triceps surae.

**Method:** This is a pilot observational study, with the aim to assess the benefit of an injection of 200 UI of uncobotulinum-toxin A in MS patients suffering from spasticity of the triceps surae which concern patient with MS with EDSS score lower than 6, needing botulinum toxin for focal spasticity of the triceps surae. The last injection, if the patient had previous botulinum treatment must be performed more than 3 months later. Outcome measures were Goal Attainment Scale, MSWS-12 scale, TUG, and 6mn Walk test and spatiotemporal gait parameters by barometric pist GaitRITE, before, 6 weeks and 3 months after the injection.

This study was approved by the local ethic comity.

**Results:** We present the result of 22 patients, with a mean age of 48.2 +/-12 years, and a mean EDSS of 4.2 (median 4.7). There was a significant benefit on injected (0.005) and non injected (0.01) step length measured by GaitRITE but not on supports distribution (0.18;0.38) especially at 3 months. It could explain the decrease of gait fatigability and the increase of speed 6mnWT (0.02) although neither TUG nor MSWS-12 were improved at 3 months after injection. 80% of the patient had reached their objective on the GAS. At 6 weeks, spatiotemporal parameters and 6mnWT were not significantly different even though we observed a significant improvement for the GAS, the MSWS-12 score ( $p=0.015$ ), and the TUG ( $p=0.003$ ).

**Conclusion:** it tends to confirm the interest of botulinum toxin A for the treatment of focal spasticity of the triceps surae with a significant improvement of gait especially on speed and also fatigability and endurance. Further studies are needed to confirm the place of botulinum toxin in this indication, but also the modalities of use in term of dosage and interval between injections. The best results on gait parameters are obtained after 3 months that is different than the results on TUG and MSWS-12.

These results support the place of botulinum toxin in the focal spasticity of the triceps surae in MS and are in concordance with the French recommendations about focal spasticity treatment. Botulinum toxin should probably be discussed early in the management of spasticity in MS patients.

**Disclosure**

nothing to disclose for every authors

**EP1812**

**Low rates of disease-modifying therapy initiation and switching after steroid treatment of patients with MS: treatment patterns from a US retrospective claims-based study**

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**Background:** In healthcare claims databases, corticosteroid use in MS patients likely indicates relapse. Failure to initiate or switch disease-modifying therapy (DMT) after relapse activity could indicate clinical inertia, in which patients may not be provided individually optimised treatment.

**Goal:** To assess the presence and impact of clinical inertia in MS patients receiving corticosteroid treatment.

**Methods:** This analysis included patients with a corticosteroid claim (as a proxy for relapse) during the 12 months prior to the most recent claim with a diagnosis of MS. Treatment patterns were assessed based on medical and pharmacy claims.

**Results:** 3972 MS patients (n=3304 covered by Medicare [MC] and n=668 covered by commercial [CM] insurance) had ≥1 claim for corticosteroids during the study period; 50% (MC) and 44% (CM) of patients received a steroid as outpatients. Among patients who were on DMT before the initial steroid treatment (n=1517 MC; n=377 CM), DMT claims after steroid were infrequent (10% MC, 16% CM). Of those who did receive DMT, the majority did so ≤60 days post-steroid. 67% (MC) and 68% (CM) of patients had a follow-up physician visit ≤30 days post-steroid, and 83% and 81% within 60 days; 19% (MC) and 17% (CM) of DMT-treated patients had an MRI ≤60 days post-steroid. Rates of post-steroid DMT switching were low (14%-18%; MC and CM) even in patients with ≥2 episodes of steroid use. In the DMT-treated MC population who switched DMT, IFNB-1a was most often the pre-switch DMT (34% and 27%, respectively, for patients with 1 and ≥2 episodes of steroid use), followed by glatiramer acetate (30% and 27%); patients most often switched to an oral DMT (88% after 1 steroid episode, 82% after ≥2 episodes). Patterns for follow-up care were similar in patients not treated with DMT prior to initial steroid; however, they were more likely than DMT-treated patients to have an ER visit (18% each in MC and CM without DMT vs 15% [MC] and 9% [CM] with DMT) or hospitalisation (11% and 9% without DMT vs 9% and 4% with DMT) ≤60 days after initial steroid. No patients newly initiated DMT ≤60 days after initial steroid.

**Conclusion:** At the time of steroid treatment, only two-thirds of MS patients were receiving DMT. Although acute relapse care and follow-up were documented, DMT initiation and switch rates were low, which may indicate clinical inertia among treating physicians. Further studies are needed to understand the factors driving these treatment patterns.

**Study support:** Sanofi

**Disclosure**

MS, LH, PI: Employees of Sanofi

AC-T, RD: Employees of Comprehensive Health Insights: A Humana Company

**EP1813**

**Managing the transition to secondary progressive multiple sclerosis: a scoping review**

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**Background:** Approximately 50% of patients with relapsing remitting multiple sclerosis (RRMS) will develop secondary progressive MS (SPMS) within 15 years of disease onset. The transition phase is characterized by a period of diagnostic uncertainty that may last several years. Evidence about transition to SPMS is scarce.

**Objectives:** The 'Managing the Transition (ManTra)' project aims to develop and test a resource for people with SPMS. As a preparatory step, we aimed to perform a literature review.

**Methods:** A scoping review was performed to map the existing literature, using the Arksey & O'Malley framework. We searched MEDLINE, EMBASE, PsycINFO, CINAHL, Google (selective search) from inception to 2017. Trial and dissertation registers were also searched for published and unpublished studies. We included primary research focused on the process of transition from RRMS to SPMS related to patients, carers or health professionals (HPs).

**Results:** Five studies fulfilled the inclusion criteria and were analysed. Of these, four (80%) were qualitative studies conducted in UK between 2013 and 2015, and one was a retrospective cohort study conducted in US in 2014, the latter aiming to characterize the transition to SPMS. The qualitative studies investigated the lived experience of adults with SPMS and documented views of carers and HPs during transition. Main themes identified pertained to reclassification of SPMS, and its consequences on patients, carers and HPs. Furthermore, possible strategies were identified to support these groups. The quality of reporting of the qualitative studies was good.

**Conclusion:** Despite the importance of this topic, only few research results have been published targeting the process of transition to SPMS, mainly focussing on qualitative studies. No interventions to empower and support patients, carers, and HPs are available and more research is needed to address this important issue. This scoping review will inform subsequent phases of the ManTra project.



## Disclosure

## Conflicts of interest

All the authors declare that they have no competing interests.

## Source of funding

The Fondazione Italiana Sclerosi Multipla (FISM) funded the study (Grant No. 2015/R/22 to AS).

### EP1814

#### Does dalfampridine trigger or worsen trigeminal neuralgia in multiple sclerosis patients?

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**Objective:** To determine whether trigeminal neuralgia (TN) emerges or worsens with the use of dalfampridine in patients with multiple sclerosis (MS).

**Introduction:** Dalfampridine (4-aminopyridine) is a broad-spectrum, voltage-dependent potassium channel blocker which improves action potential conduction in demyelinated motor axons. Several studies showed that dalfampridine is effective in treating gait impairment in MS patients.

**Methods:** Thirty one clinically definite MS patients using dalfampridine for gait impairment participated in the study. The variables examined included age, gender, type of MS, and the existence of trigeminal neuralgia.

**Results:** Nineteen (61%) of the patients were women and twelve were men. 55% of the patients were diagnosed as secondary progressive, 29% relapsing remitting, and 16% primary progressive MS. Of the thirty one patients, five (16%) had trigeminal neuralgia. Two of these patients had preexisting TN signs, which worsened following the use of dalfampridine and became unbearable. Three patients began to suffer from TN signs after the administration of the treatment. Brain MRIs showed no structural pathologies, rather than demyelinating lesions of the brainstem. All patients were treated with gabapentine. Symptomatic treatment with gabapentine did not result in the reduction of the severity of the pain thus dalfampridine ceased in three patients. Discontinuation of dalfampridine controlled the pain well in two patients, but one patient continued to have severe pain.

**Discussion:** Evidence from this study suggests the use of dalfampridine may worsen preexisting TN or trigger de novo TN symptoms in MS patients.

## Disclosure

Sila Usar Incirli: nothing to disclose

### EP1815

#### Effect of fampridine on the manual functions of patients with multiple sclerosis: difference between cerebellar and pyramidal dysfunction

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Fampridine may influence upper limb dysfunction, such as strength and even in upper limb tremor. In this study we aimed to assess the effect of Fampridine treatment on upper limb function of persons with multiple sclerosis (PwMS). We also compared the effect of Fampridine on cerebellar and pyramidal dysfunctions. PwMS aged 18 to 60 years followed-up at the Dokuz Eylul MS Center eligible to Fampridine treatment due to ambulatory disabilities and that in addition presented complains in manual function such as lack of coordination, deficits in fine motor skills, difficulties with dressing, writing and/or buttoning, were invited to participate in this study.

A total of 168 patients (109 female) were included in the study. Nine patients were excluded from the study due to early discontinuation of Fampridine because of side effects, or personal considerations. One hundred fifty-nine patients were followed up to 12 months and 151 patients up to 24 months after initiation of the treatment and are included in this study. Seventy-seven (50 female) healthy controls (HCs) were also included. No significant statistical differences between demographic characteristics of these two groups were found. Manual functions were evaluated by 9 Hole Peg Test (9HP) and visual analog scale (VAS) for hand functions. For evaluating the disability EDSS was performed. Cerebellar and pyramidal functional system (FS) scores were compared.

9HPT improved by 19.8% after 1 month of treatment ( $p=0.004$ ). Improvement was sustained on month 3, 6, 12 and 24. HC 9HPT results were also improved (3.6%) but not statistically significant ( $p>0.05$ ). VAS improved by 18% after 1 month of treatment ( $p=0.02$ ). When comparing FSs, patients with 0 to 2 cerebellar FS scores ( $n=76$ ) were significantly more improved (23.5%) than patients with 3 and up cerebellar FS scores (9.2%) ( $p<0.0001$ ).

The results of this study suggest that Fampridine improves manual function of PwMS. Patients with cerebellar dysfunction were also improved but not as much as patients without marked cerebellar impairment. Patients complains in manual functions due to pyramidal dysfunction seems to be more improved in Fampridine treatment than cerebellar dysfunction.

## Disclosure

Serkan Ozakbas: nothing to disclose

Turhan Kahraman: nothing to disclose

Bilge Piri Cinar: nothing to disclose

### EP1816

#### Effect of a standardized physical therapy program on objective and subjective balance in people with multiple sclerosis: a single-group, pretest-posttest study

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**Background:** Imbalance is a frequent problem in MS and contributes to considerable patient burden, affecting outcomes such as independence, community participation and quality of life.

**Objective:** To evaluate the effect of a standardized exercise programme on objective and subjective balance in people with mild to moderate multiple sclerosis (MS).

**Methods:** Prospective data were obtained from all patients with an EDSS  $\leq 6.5$  who were admitted and completed a rehabilitation period at the Neurorehabilitation Unit of Cemcat during the second semester of 2016. Patients carried out a 3 days per week 5 months long outpatient rehabilitation program. The standardized physical group therapy programme included three major components modified according to each patient specific impairment and functional needs: muscular training, balance training and gait re-education strategies. Outcome measures included the Berg Balance Scale (BBS), the Timed Up and Go Test (TUG) and the Activities-specific Balance Confidence Scale (ABC) measured before and after the rehabilitation programme. Data on self-reported falls (indoors and outdoors) was collected retrospectively by interview

**Results:** Fifty people with MS (32% men) were included with a mean age of 51.44 years and a median EDSS of 4.5. Fifty-four percent had relapsing remitting MS, 25% had secondary progressive MS, 18% had primary progressive MS and one patient, 2%, had a transitional form.

All three clinical outcome measures demonstrated statistically significant improvements after the intervention (BBS change of means: from 46.14 to 48.78,  $p < 0.05$  - TUG change of means: 15.36s to 13.88s,  $p < 0.05$  - ABC change of means: 46.40 to 52.65,  $p < 0.05$ ). Percentage of participants improving in each of the outcome measures was: BBS (44%), TUG (18%), and ABC (54%). A reduction of fallers and falls, statistically significant, was also reported between the pre and post intervention period.

**Conclusions:** Our findings are in line with previously published results providing evidence that targeted physiotherapy interventions can positively affect balance performance and decrease falls in PwMS. Improvement in static balance, dynamic balance and self-related perception of imbalance was statistically significant. A decrease in the number of falls and the proportion of fallers pre and post-intervention was also noted.

## Disclosure

The authors have nothing to disclose as to the present work

## EP1817

### Physical activity and sedentary behavior in MS: impact on dissociable correlates of cognitive functioning

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Moderate-to-vigorous physical activity (MVPA) is increasingly being recommended to promote cognitive health in people with MS (PwMS). A higher level of MVPA in PwMS is associated with improved information processing efficiency, especially in those with lower disease severity scores. However, the construct of information processing efficiency, including both working memory and processing speed is poorly defined, leading to challenges in interpreting these results for PwMS. In the current study, our goal was to examine the differential contributions of MVPA and sedentary behavior in explaining variance in the constructs of working memory and processing speed in PwMS. Forty-four individuals with relapsing-remitting multiple sclerosis were recruited

for the current study. All participants were administered the subtests comprising the Working Memory and Processing Speed Indices of the Wechsler Adult Intelligence Scales (WAIS-IV) to quantify theoretically sound metrics of working memory and processing speed, respectively. Additionally, all participants wore an Actigraph accelerometer for a 7-day period, which was then used to quantify both MVPA and sedentary behavior. Our results provided evidence for a double dissociation in the associations between physical activity, sedentary behavior and cognitive functioning. Specifically, MVPA was associated with the Working Memory Index, specifically the mental manipulation cluster, such that a higher level of MVPA in PwMS was associated with better performance on tasks of working memory. In contrast, sedentary behavior in PwMS was negatively associated with the Processing Speed Index, such that higher engagement in sedentary behavior was associated with poor performance on measures of processing speed. Future directions for the study include analyzing resting-state data on all participants using graph theory methodology to determine neural correlates of the observed associations. Given the physical limitations experienced by PwMS, these results evince support for the importance of both MVPA as well as reduced sedentary behavior in promoting cognitive health in MS.

## Disclosure

Ruchika Prakash: nothing to disclose

Alisha Janssen: nothing to disclose

Heena Manglani: nothing to disclose

## EP1818

### Virtual reality training or physical activity? Which one is more effective in reducing pain among persons with multiple sclerosis? A randomized controlled trial

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**Background:** Multiple sclerosis (MS) is the most common disabling disease of CNS among young adults. Pain is a common symptom among people with MS (pwMS). Despite a wide range of pain management interventions that have been applied in pwMS, still many of them are experiencing moderate to severe pain sometimes during their disease course. The benefits of physical activity for pwMS have been recognized. However, not all of them are able to attend physical activity sessions due to different barriers they may face. In recent years, virtual reality (VR) has become popular in clinical settings as an innovative pain distractor technique that can be used safely at home by pwMS and may propose alternative benefits.

**Goals:** The objective of this study was to investigate the effectiveness of VR intervention (VR) in comparison to combined physical activity & VR training (PA&VR), physical activity alone (PA), and no training in reducing pain in pwMS.

**Methods:** This was a randomized controlled trial (RCT). Sixty women with MS (EDSS  $< 4$ ) were randomized to one of the VR (Nintendo Wii), PA, PA&VR, or control groups (15 per each group). The experimental groups performed the assigned intervention for 12 weeks (2 sessions per week, each 40 minutes). Outcomes included bodily pain intensity (pain subscale of RAND-36), pain severity (0-10 NRS), pain distribution (Margolis drawing rating

system), and pain duration and frequency measured at baseline and 12 weeks later. Fatigue (Vitality subscale of RAND-36), MS severity (EDSS) and mood (0-10 NRS) were considered as explanatory variables.

**Results:** The mean age of participants was  $43 \pm 6.2$  and mean years since diagnosis was  $5.6 \pm 9.0$  years. The majority of participants (82%) were in relapsing-remitting course of MS. There were significant differences among study groups on pain related outcomes ( $p < 0.05$ ) except for pain frequency. The post hoc analysis further showed that the PA&VR did better in all pain related outcomes followed by either PA or VR. Mood highest change was seen in VR followed by PA&VR; while fatigue highest change was seen in PA followed by followed by PA&VR and VR group.

**Conclusions:** The present study identifies VR distraction techniques as promising non-pharmacological approach for pain management in pwMS due to its novelty and distraction nature. The VR alone showed advantage over no therapy in the management of pain in pwMS; however, it got third place after PA&VR and PA.

### Disclosure

Author declares no conflict of interest.

### EP1819

#### Safety and efficacy of botulinum toxin A in MS patients with intractable chronic migraine

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**Background:** MS patients have an increased incidence of headaches. Headache in MS commonly could be both presented as episodic or chronic migraine. Chronic migraine occurring on more than 15 days per month for at least 3 months and a daily duration of at least 4 hours, is considered with possible efficacy of botulinum toxin A.

FDA approved botulinum as a treatment for muscle relaxation in MS patients in 2010 so its utilization considered to be safe. We used botulinum A in a cohort of MS patients with chronic and intractable migraine.

**Method:** 302 out of 1200 patients with definite MS taking standard MS treatment, complained headache fulfilling migraine criteria. 25 out of 302 patients didn't respond to the common oral migraine treatment defined as below 30% response. We injected botulinum toxin A in 31 anatomical standard points on skull, reporting frequency, intensity, duration and medication rescue.

**Results:** All the cases were female with the mean age of 30.20, a mean disease duration of 55.72 months and mean EDSS of 1.5. Mean migraine frequency was 4.48 per week, intensity 78.57% out of 100 and duration of 9.96 hours. Standard oral migraine treatment response rate in these 25 patients was 21.78%.

Before injection the mean migraine frequency was 6.28 per week, intensity 94.8% and duration 10.36 hours. After injection the mean frequency 1.16 per week, the mean intensity 26 out of 100, and the duration was 2.24 hours. The mean Botulinum dosage was 1.36, equal to 680 unit.

**Conclusion:** Botulinum toxin A should be considered a safe and effective treatment in MS patients with intractable chronic migraine.

**Keywords:** MS, Botulinum toxin, intractable chronic migraine, headache

### Disclosure

No conflict of interest

### EP1820

#### Cognitive problems in people with multiple sclerosis: a mixed methods study on the provision and perceived effectiveness of cognitive rehabilitation

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**Background:** Two-thirds of people with multiple sclerosis (MS) experience cognitive problems associated with attention and memory. Cognitive rehabilitation to improve such cognitive deficits and help people cope with these problems has emerged as a potential treatment approach. However, the evidence regarding its effectiveness is mixed and cognitive rehabilitation is not routinely provided in the UK. Therefore, this study addresses two main questions: What are patients' perspectives on the effectiveness of cognitive rehabilitation? How is cognitive rehabilitation delivered nationally?

**Method:** This study comprises three phases. Phase 1 was a meta-synthesis agglomerating findings of qualitative studies examining patient perspectives of the effectiveness of cognitive rehabilitation programmes. Phase 2 investigates patient perspectives, using semi-structured interviews, of a group-based rehabilitation programme. Phase 3 is a survey examining the provision of cognitive rehabilitation nationally.

**Data analysis:** The meta-synthesis and interview data were analysed using thematic analysis.

The survey will be analysed using descriptive statistics.

**Results:** The meta-synthesis highlighted the perceived benefits of cognitive rehabilitation in people with MS. Participants reported benefits in cognitive function and other areas related to their quality of life. They reported improved mood and quality of their relationships, an increase in confidence and perseverance, and the programme helped them to change their perceptions of their condition. The group-component was often referred to as a beneficial aspect as it helped patients to experience a sense of community and support. Preliminary results of the second phase suggest that people do manage better after a group-based rehabilitation programme compared to people who have not participated in cognitive rehabilitation. The national survey is underway.

**Conclusion:** The knowledge and insight generated from each phase of this study will provide an overview of the provision and perceived impact of cognitive rehabilitation. This may inform and improve current practice and services for people with MS.

### Disclosure

Conflict of interest: None

Source of funding: This study is supported by the MS Society PhD studentship 'Delivering cognitive rehabilitation to people with MS'



## EP1821

**De novo convulsive status epilepticus in multiple sclerosis patients treated with dalfampridine**

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**Background:** Dalfampridine-ER (DAL) is a broad-spectrum voltage-gated potassium channels blocker, that is indicated in multiple sclerosis (MS) to improve nerve conduction in demyelinated axons. Seizures are a known side effect of DAL, which is contraindicated in patients with a history of seizures.

**Objective:** 3 case-reports about MS patients (Pts) with «de novo» convulsive status epilepticus (CSE) probably related to DAL administration.

**Methods:** 3 Pts with secondary progressive MS (2 women (Pt1:26 years, Pt2:60 years) and a man (Pt3:48 years), were admitted because of CSE. Their medical charts recorded: mean age at MS diagnosis: 22 years-old, last average EDSS 7 with spastic paraparesis, no history of seizures or renal impairment.

Pt 1: She observed a treatment with DAL, 10 mg tid, introduced 3 years ago, with baclofen and tamsulosine. She presented a tonic clonic seizure. Intravenous (IV) diazepam was given, but myoclonus of left hemiface persisted. IV phenytoin then IV phenobarbital was given because of persistent EEG focal temporal SE. Pt 2: Treatment with DAL was introduced 4 years ago, with oxybutinin, baclofen and qizenday ATU. She presented continuous myoclonic jerks involving the right side of the body with impaired awareness. IV diazepam then IV phenytoin then IV levetiracetam were indicated because of persistent EEG focal ictal activity.

Pt 3: DAL was introduced 2 days ago, with baclofen. He presented with five tonic-clonic seizures in between impaired consciousness persisted. IV diazepam led to the resolution of CSE.

Biological tests were normal. Brain MRI showed diffuse cortical and subcortical atrophy, without active inflammatory lesion.

**Results:** All 3 Pts presented with CSE that were attributed to DAL, which was discontinued. All Pts were on baclofen at admission, which was tapered down. Anti-epileptic drug was introduced: phenytoin and eslicarbazepine (Pt1), levetiracetam and phenytoin (Pt2). Third Pt presented 9 months after a new tonic-clonic seizure, and levetiracetam was introduced. No DAL compliance deviations were identified.

**Conclusion:** These case-reports illustrate that «de novo» CSE is a potential complication of MS patients treated with DAL. All Pts had important cortical and subcortical demyelination on brain MRI, but no renal impairment that would have enabled lowered renal excretion of DAL. All Pt had concomitant therapy with baclofen, a proepileptic drug. Potential interaction between these 2 drugs may have precipitated CSE in our Pts.

**Disclosure**

CLF has participated to scientific boards for Biogen, Roche, Novartis, Merck, medDay. Others authors disclosed no affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias.

## EP1823

**A new cognitive-linguistic patient report tool: correlation with the BICAMS**

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**Background:** Persons with Multiple Sclerosis (pwMS) each experience unique constellations of cognitive symptoms. Standardized assessment tools, such as the BICAMS, do not offer a pwMS the opportunity to express explicit examples of functional challenges in day to day routines. Speech-Language Pathologists (SLPs) treat the symptoms of cognitive impairment, but require information from patients about cognitive challenges the pwMS may be experiencing. A Multiple Sclerosis Cognitive-Linguistic Checklist (MSC-LC) was developed by a SLP at a Comprehensive MS Care Center in the U.S., and was revised through a Delphi Protocol with patients at the Comprehensive Care Center acting as the “experts” on the panel (unpublished). Content, format and appearance of the MSC-LC was generated with direct input of pwMS managing the disease progression on a daily basis. In order to provide a complete clinical picture of the pwMS, both objective and subjective data need to be collected. The MSC-LC has been in clinical use in conjunction with the BICAMS for approximately one year.

**Goal:** In order to improve the quality of patient care...determine if scores on the MSC-LC in correlate with the BICAMS when collected during the same assessment. As these are clinical data, there are no exclusions from these calculations.

**Results:** The MSC-LC contains 20 questions. Of the individual questions:

**Eleven** correlate with the SDMT at a value of  $p < .05$ ; (55%)

**Thirteen** correlate with the CVLT2 at a value of  $p < .05$ ; (65%)

**Ten** correlate with the BVMTR at a value of  $p < .05$ ; (50%)

Correlations are as follows when the 20 questions are grouped by content:

Language Retrieval - **SDMT** ( $p=0.0061$ ), **CVLT2** ( $p=0.073$ ), **BVMTR** ( $p=0.057$ )

Managing Distractions - **SDMT** ( $p=0.011$ ), **CVLT2** ( $p=0.001$ ), **BVMTR** ( $p=0.057$ )

Conversation - **SDMT** ( $p=0.021$ ), **CVLT2** ( $p=0.0064$ ), **BVMTR** ( $p=0.066$ )

Information Management - **SDMT** ( $p=0.0019$ ), **CVLT2** ( $p=0.0055$ ), **BVMTR** ( $p=0.0007$ )

Organization - **SDMT** ( $p=0.0013$ ), **CVLT2** ( $p=0.0051$ ), **BVMTR** ( $p=0.454$ )

**Conclusion:** The majority of questions on the MSC-LC are correlated with standardized measures of cognitive impairment (BICAMS). Future directions- determine if ruling out groups with optic neuritis and/or non-native English speakers will change the correlations.

**Disclosure**

Lori Ann Kostich M.S. CCC-SLP, MSCS has nothing to disclose.

Dorothy Wakefield M.S. PStat has nothing to disclose.

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## EP1824

**At-home transcranial direct current stimulation (tDCS) improves mood in multiple sclerosis: results from a randomized, sham-controlled trial**

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**Background:** tDCS is a therapeutic approach that applies low amplitude currents (typically 1-4 mA) through scalp electrodes with the goal of altering the resting state of neurons for potential therapeutic benefit. A growing body of evidence indicates that tDCS applied to the left dorsolateral prefrontal cortex (DLPFC) may be beneficial in the treatment of depression, a common comorbidity with multiple sclerosis (MS). The DLPFC is a neurobiological substrate related to both aspects of mood and cognition. We tested mood outcomes in a recently completed randomized sham-controlled and double blinded trial of tDCS in MS participants.

**Methods:** Participants with MS were recruited to participate in a randomized, sham-controlled trial of tDCS testing remote (at-home) delivery of treatment. Supervised in real time through videoconferencing, participants completed 20 treatment sessions from home over four weeks. Participants were randomly assigned to active (2.0mA left anodal) or sham tDCS using the DLPFC montage. Sessions were administered for 20 minutes during which participants also completed cognitive training exercises each session. Participants completed self-report questionnaires at baseline and study end visits, including the Positive and Negative Affect Schedule or PANAS to provide specific components of mood.

**Results:** Participants receiving active tDCS (n=14) reported a significant increase in PA and decrease in NA by study end (mean changes of  $4.4 \pm 6.2$ ,  $p=0.02$  and  $-5.7 \pm 5.9$ ,  $p=0.003$ , respectively). Sham-treated participants (n=10) did not show significant change in either positive or negative affect (mean changes of  $4.4 \pm 6.2$  vs  $-0.6 \pm 6.2$ ,  $p=0.068$  and mean changes of  $-5.7 \pm 5.9$  vs  $-2.0 \pm 5.0$ ,  $p=0.111$ , respectively).

**Conclusions:** Twenty sessions of tDCS, administered at home using a telerehabilitation protocol, significantly increases positive affect and decreases negative affect in participants with MS. Findings support the role of DLPFC in regulating mood and warrant a clinical trial for the treatment of MS-related depression.

**Disclosure**

Michael Shaw has nothing to disclose.  
Bryan Dobbs has nothing to disclose.  
Natalie Pawlak has nothing to disclose.  
William Pau has nothing to disclose.  
Leigh Charvet has nothing to disclose.

## EP1825

**Investigation of the effects of computer assisted cognitive rehabilitation in multiple sclerosis patients: a randomised-controlled study**

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**Objective:** The objective of this study was to investigate the efficacy of a computer assisted cognitive rehabilitation program with focus on memory, attention and executive functions in relapsing-remitting multiple sclerosis patients (RRMS) with mild cognitive impairment; and to determine the compliance of patients to computer-assisted cognitive rehabilitation.

**Methods:** RRMS patients with mild cognitive impairment followed at our neurology clinics were included in the study. The study was designed as a prospective, randomised-controlled and single-blind study. Study and control subjects were evaluated using standardised mini-mental test, Beck depression inventory, and Rao's Brief Repeatable Battery for neuropsychiatric diseases.

**Results:** Results demonstrated that error point on Symbol Digit Modalities Test (SDMT) was reduced with application of computer assisted cognitive rehabilitation, while increased in controls; Selecting Reminding Test (SRT) short term memory results were significantly increased with application of computer assisted cognitive rehabilitation; and results of Stroop test also revealed that study subjects made less corrections compared to controls. Improved results were also obtained in Paced Auditory Serial Addition Test (PASAT), SDMT, and Word List Generation (WLG)-category tests in study group compared to the control group although not to a statistically significant degree.

**Conclusion:** Computer-assisted cognitive rehabilitation applications aimed at improving specific cognitive domains proved beneficial in the improvement of cognitive domains including attention, memory and executive function in patients with multiple sclerosis.

**Disclosure**

Nothing to disclose

## EP1826

**Implementing cognitive rehabilitation for people with MS: translating research into clinical practice**

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**Background:** Memory, attention and executive function are commonly reported cognitive problems by people with multiple sclerosis (MS). These problems can severely affect quality of life of the individual, their family and carers. Although the effectiveness of cognitive rehabilitation programmes has been evaluated in clinical trials, inadequate reporting of the content of the interventions may prevent clinical implementation.

The overall aim of this research is to develop a clinician-informed, evidence-based checklist to guide researchers to better report cognitive rehabilitation studies in order to increase clinical impact.

**Methods:** This mixed-methods research consists of three stages: (i) A systematic review and narrative synthesis of the literature on the content and quality of reporting of cognitive rehabilitation for people with MS;

(ii) A content analysis and time-sampling analysis of video recordings of an intervention delivered in an ongoing multi-centre trial of Cognitive Rehabilitation of Attention and Memory in MS

(CRAMMS), focusing on the content of treatment sessions. Findings from these two stages will form stage three;

(iii) A modified Delphi consensus study with healthcare professionals and researchers who work with people with MS, to establish key aspects of the intervention that researchers should report for the clinical translation of cognitive rehabilitation. This will result in a consensus checklist.

#### Results:

(i) 52 studies involving various types of MS and techniques to improve difficulties with memory, attention and executive function were included in the systematic review. The results showed that important features of cognitive rehabilitation were not reported well. For example: whether participants were treated individually or in a group was only reported in 46% of the papers; the intervention techniques used and how they facilitated improvement of cognitive problems and/or function was only reported in 38% of the papers.

(ii) Data analysis of the content of the CRAMMS intervention is in progress.

(iii) The Delphi consensus study will commence in August 2017.

**Conclusion:** The development of a clinician-informed, evidence-based checklist may enable researchers to report important aspects of complex interventions. This may improve potential clinical uptake of effective interventions.

#### Disclosure

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The authors declare no other conflict of interest.

#### EP1827

##### Changes in activities of daily living by Fampyra

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**Background:** In patients with multiple sclerosis (PwMS), there is an evidence that Fampyra LR improves walking and also the performance of activities of daily living (ADL). Consequently, we investigated the responsiveness of Fampyra LR in terms of performance and satisfaction of meaningful and self-chosen ADLs by using the Canadian Occupational Performance Measure (COPM).

**Method:** There were 111 consecutive PwMS who were referred by neurologists to Occupational therapy (OT). They were candidates for treatment with Fampyra LR, and were independently followed within OT. PwMS were assessed by the COPM before starting treatment with Fampyra LR and reassessed after two weeks. COPM (Law et al, 1991) is standardized and well-validated semi-structured interview. It assesses patients' perception and satisfaction of purposeful, meaningful and self-chosen ADLs. It is therefore patient-centred assessment. As part of the interview process, patients are asked to score their current level of performance and satisfaction with their performance of ADLs. Scores are within the range from 1-10; 1 relates to great difficulty or not satisfied and 10 to no difficulties or completely satisfied. SPSS was used for analysis.

**Results:** In total, 106 PwMS completed the study; there were 30 male / 81 female, average age was  $51 \pm 11$  years and average EDSS was  $5.5 \pm 1.1$ . The average initial COPM performance score was

$4.6 \pm 2.2$  and the average reassessment score was  $6.2 \pm 2.3$ . This difference was significantly important ( $p < 0.001$ ). The average initial COPM satisfaction score was  $5.1 \pm 2.3$  and the average reassessment score was  $6.6 \pm 2.5$ . This difference was significantly important ( $p < 0.001$ ).

**Conclusion:** The ADL performance, measured in terms of PwMS' perception and satisfaction with their performance of meaningful and self-chosen ADLs has improved after Fampyra LR treatment. Further relation of this improvement with walking changes could additionally clarify this topic.

#### Disclosure

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Sasa Segar has nothing to disclose.

#### Quality of life

#### EP1828

##### Does mindfulness, meditation and progressive muscle relaxation reduce stress in people with multiple sclerosis?

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**Background and aim:** The National Institute for Health and Care Excellence clinical guidelines, together with the global consensus document 'Brain Health', acknowledge that modification of lifestyle factors contribute to the holistic care of people with Multiple Sclerosis (MS). While people with MS often report stressful life events as a precursor to developing MS, and despite increasing evidence of perceived stress as a risk factor for disease activity, the evidence for effectively managing stress in this population is limited. This study examined the effect of an educational program that incorporates progressive muscle relaxation (PMR), meditation and mindfulness exercises (ME), on a population of people with MS over a six month period.

**Method:** 100 people with relapsing remitting MS were randomly assigned to receive:

- 1) stress management education (SME) or
- 2) wait list (WL).

The SME group received four one-on-one sessions learning PMR, meditation and ME and asked to perform PMR, meditation and ME for 5-7 days of the week for six months, which was monitored by diary. The primary outcome was change in perceived stress as measured by: the stress Visual Analogue Scale (sVAS), the stress component of the Depression, Anxiety and Stress Score (DASS21), and cortisol levels collected at baseline and four weeks. Cortisol levels were ascertained by saliva samples collected at three time points over a 24-hour period and then averaged. The secondary outcome measure was change in quality of



life as measured by the Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL).

**Results:** None of the parameters evaluated changed between pre and post SME ( $p \leq 0.05$ ). Mean scores for sVAS at baseline and follow up 1 (4 weeks) were 4.8 and 4.5 for SME and 3.7 and 4.1 for WL. Mean scores for stress component of the DASS21 were 15.3 and 13.7 for SME and 13.8 and 12.6 for WL. Mean cortisol levels changed were 7.3 nmol/L to 7.6 nmol/L for SME and 5.1 nmol/L to 7.6 nmol/L for WL. Mean MusiQoL scores were 65.2% and 67.3% for SME and 66.9% and 70.8% for WL. Study outcome was potentially limited by intervention adherence; good adherence (5-7 days per week), reasonable adherence (2-4 days per week) and poor adherence (0-1 day per week) to SME was undertaken by 24%, 19% and 45% respectively.

**Conclusions:** Results indicate that SME does not significantly improve levels of stress or quality of life in people with MS. Future studies could include barriers to adherence.

### Disclosure

Susan Agland: Accepted travel compensation from Novartis, Biogen and Merck Serono. Her institution receives the honoraria for talks and advisory board commitment from Bayer Health Care, Biogen, Genzyme Sanofi, Merck, Novartis, Teva and Roche.

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### EP1829

#### The effectiveness of a diverse manner of functional electrical stimulation on balance, gait and quality of life in people with multiple sclerosis

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**Background:** Although a recently developed alternative to solve foot drop-the functional electrical stimulation (FES)- seems to be a promising treatment method, there is only one study which showed *therapeutic effect* in pwMS. To our knowledge only 3 studies compared or connected FES and physiotherapy.

**Objective:** Our aim was to investigate the effectiveness of 2 different ways of using FES combined with physiotherapy and Walkaide to learn which method produced better outcomes for balance, mobility, gait and quality of life in pwMS.

**Methods:** 43 pwMS were divided into 3 groups which underwent:

- 1) physiotherapy + FES in training mode for 2 months;
- 2) FES for daily use for 2 months;
- 3) 2 months physiotherapy before 2 months Walkaide for daily use.

Tests examined mobility (Rivermead mobility index, Performance scale Mobility, Five times Sit to Stand test), balance (Berg Balance

Scale, Timed Up and Go Test, Dynamic Gait Index), gait (Timed 25 - foot Walk Test, 2 - Minute Walk Test). We also administered the following questionnaires: Multiple Sclerosis Walking Scale 12, The Activities - specific Balance Confidence Scale, Multiple Sclerosis Impact Scale-29 (MSIS29), EuroquoL - 5 dimensional - 5 levels (EQ - 5D - 5L) were assessed without FES 4 weeks before baseline, at baseline, after treatment and 2 months after treatment.

**Results:** We found a significantly positive effect of combination of FES and physiotherapy on Berg balance scale in group 1 and 3 ( $p = 0.007$ ; 0, 04 resp.). Group 1 showed significant positive effects in EQ-5D-5L on mobility, usual activities, pain/discomfort and health; and in MSIS29; group 3 showed significant positive effect in EQ-5D-5L on mobility.

**Conclusion:** Combining FES with facilitation physiotherapy has a positive effect on balance and quality of life in pwMS.

### Disclosure

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### EP1830

#### Psychopathological symptoms have a profound effect on the quality of life of multiple sclerosis patients

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Zboznovits<sup>2</sup>, Z. Burány<sup>2</sup>, É. Langane<sup>1</sup>, L. Vécsei<sup>1,3</sup>, K. Bencsik<sup>1</sup>

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**Introduction:** Multiple sclerosis (MS) not only causes somatic disability but often leads to psychopathological symptoms such as cognitive impairment (CI), depression and fatigue. Benedict et al (2005) showed that CI, depression and fatigue worsen the patients' QoL as much as the physical disability. This study aimed to assess the impact of these symptoms on the patients' QoL during a 1-year follow up.

**Patients and methods:** We recruited 178 relapsing-remitting and CIS patients to our study from two major MS clinics in Hungary (Szeged, Budapest); 52 were man, 126 women. We utilized the BICAMS battery for cognitive screening, the MSQoL-54 for the assessment of QoL, the FIS questionnaire for measurement of fatigue, and the BDI-II for the assessment of depression. The first evaluation was carried out in 2014-2015, the follow-up period was in 2015-2016, 1-year after the initial tests. For statistical analysis, we developed a linear mixed-effects model.

**Results:** The mean age at the follow-up of our patients was  $44.8 \pm 11.4$  years, the mean disease duration was  $15.3 \pm 8.0$  years and median EDSS score was 2.0 (range: 0-6.0) points. In our model we found, that the appearance of fatigue significantly ( $p < 0.05$ ) reduces the patients' QoL in all 14 dimensions measured by the MSQoL-54. Similarly, the appearance depression has a significant ( $p < 0.05$ ) impact on the patients QoL on 13 of 14 dimensions (except for the "Change in health" dimension;  $p = 0.287$ ). The appearance of CI does not have such a wide impact, but it significantly reduces the patients QoL in the "Physical functioning",

“Social functions” and “Cognitive functions” dimensions ( $p < 0.05$ ), even if the rate of cognitive impairment is mild.

**Discussion:** Our findings strongly suggest that the psychopathological changes are heavy factors in determining MS patients' quality of life. Fatigue and depression have particularly strong and wide effects. Also, even mild CI seriously impacts the patients' quality of life on both the social and the physical level.

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### EP1831

#### How to improve self-management in multiple sclerosis?

##### Directions of psychological interventions

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**Background:** Self-management of chronic illness is a key component of patients' active participation in treatment process and has been found to be associated with better quality of life, reduced disability and number of complications, improved outcomes and lower costs of treatment. So far, correlates of self-management in multiple sclerosis (MS) have not been subjected to extensive empirical research. An increased understanding of these correlations may help clinicians to identify individuals at an increased risk of poor self-management skills, take positive action towards activating the patient and implementing effective rehabilitation interventions.

**Purpose:** The aim of this study was to verify if potentially modifiable cognitive perceptions, such as self-efficacy, optimism, acceptance of illness and health locus of control are the correlates of self-management in MS.

**Methods:** The cross-sectional study included 382 patients with MS, who completed Multiple Sclerosis Self-Management Scale - Revised, and a set of questionnaires measuring self-efficacy, optimism, acceptance of illness and health locus of control. Demographic and clinical characteristics of the participants were collected with a self-report survey. Correlation and regression analyses were conducted to determine relationships between the variables.

**Results:** A hierarchical multiple regression revealed that four variables: health control - power of others

( $b = 0.42$ ,  $p \leq 0.001$ ), optimism ( $b = 0.27$ ,  $p \leq 0.01$ ), health control - internal factors ( $b = -0.11$ ,  $p = 0.017$ ) and self-efficacy ( $b = 0.11$ ,  $p = 0.031$ ), were significant correlates of self-management in our study group. These variables explained 27% of variance in the dependent variable. Moreover, correlations between self-management and other measured variables were obtained.

**Conclusions:** Self-management of patients with MS is associated with perception that health professionals and family members control their health, higher self-efficacy, optimism, and surprisingly, lower perception of personal control over one's state of health. Our study indicates the key role of the physicians in the process of motivating the patient with MS for self-management activities and produce new knowledge for potential psychological intervention aimed at improving patient's self-management.

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Wilski: nothing to disclose

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Kocur: nothing to disclose

Broła: nothing to disclose

### EP1832

#### The relationship between diagnosis acceptance, self-concept, and mental health outcomes in individuals with multiple sclerosis

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**Objective:** This study was concerned with examining depressive and anxiety symptoms, overall self-concept and physical self-concept amongst individuals with multiple sclerosis (MS) and determining how these differed between individuals with high and low MS diagnosis-acceptance. The role of MS illness duration was also evaluated.

**Methods:** 329 individuals with MS completed the an online questionnaire incorporating the Depression, Anxiety and Stress Scale (DASS-42), assessing depressive and anxiety symptoms, Acceptance of Chronic Health Conditions Scale (ACHC), assessing MS diagnosis acceptance and the Tennessee Self-Concept Scale (TSCS-2), investigating overall self-concept and physical self-concept.

**Results:** As predicted, high MS diagnosis acceptance was significantly associated with higher overall self-concept and physical self-concept, whilst low MS diagnosis acceptance was significantly associated with lower overall self-concept and higher depressive and anxiety symptoms. MS duration was significantly positively associated with overall self-concept. Contrary to predictions, there were no significant relationships between MS duration and physical self-concept or depressive and anxiety symptoms.

**Conclusion:** Results of the current study suggest that displaying high MS diagnosis acceptance is associated with positive outcomes for individuals with MS, including lower depressive and anxiety symptoms and higher overall and physical self-concept. Further research should continue to explore MS diagnosis acceptance as it appears to confer positive benefits to individuals, who

have otherwise been shown to experience high rates of depressive and anxiety symptoms and low self-concept.

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Natalie Ward: nothing to disclose.

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### EP1833

#### Effects of physical training on multiple sclerosis patients: a longitudinal study

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<sup>1</sup>Adapted Training and Performance Research Group, <sup>2</sup>Clinical and Biological Sciences, University of Turin, Torino, Italy

**Aim:** The investigation of the effects of a 30 seconds static stretching protocol, Pilates® and resistance training with elastic bands on muscle strength, rachis morphology, flexibility and body balance among RRMS patients.

**Methods:** Twenty-two subjects with relapsing-remitting multiple sclerosis (RRMS, EDSS ≤ 6) were randomly divided into 3 groups (8, 7, 7 subjects) and performed 16 weeks of training as follows. Static Stretching group: 2 sessions/week, 3 sets of 30 seconds for each exercise. Elastic group: 2 resistance training sessions/week, 3 sets of 10 repetitions. Pilates® group: 2 sessions/week, 2 sets of 8 repetitions for each exercise. Stabilometry, rachis morphology, sit and reach, and sit to stand tests were executed three times: T0, after a month of learning training protocols, to identify the initial situation; T1, two months after T0, to evaluate the effects brought about by the first eight weeks of training; T2, two months after T1, to evaluate the effects brought about by sixteen weeks of training.

**Results:** Static Stretching group. Spinal Mouse® (inclination line between ThSp1 and S1 from a standing position): T0 vs T2, -55%, ES = 0.67; Sit and Reach test: T0 vs T2, +15%, ES = 0.36. Elastic group. Stabilometry with eyes open: T0 vs T1, -51%, ES = 0.52; stabilometry with eyes closed: T0 vs T1, -52%, ES = 1.69; sit to stand test: T0 vs T2, +39%, ES = 1.83. Pilates group. Sit and Reach test: T0 vs T2, +15%, ES = 0.4; Sit to Stand test: T0 vs T2, +31%, ES = 1.21.

**Conclusions:** Static stretching, Pilates® and resistance training are believed valid to improve the motor control of the rachis, body flexibility and the performance in the Sit to Stand test. Hence, it is possible to hypothesize an increment in autonomy in the daily life of people affected by RRMS brought about by this three protocols.

### Disclosure

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### EP1834

#### Effects of multilateral exercises on motor skills in multiple sclerosis: a longitudinal study

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**Aim:** The aim of this study is to evaluate the effect of adapted physical activities with micro-loads, elastic bands and balance exercises compared with the Pilates® method on muscle strength, flexibility and body balance in Multiple Sclerosis patients.

**Methods:** Eighteen people with Multiple Sclerosis participated in this study. Subjects were randomly assigned to a Multiple Neuromuscular Stimulation Group (10 participants, age 69±10 years; weight 72±12 kg, height 171±7 cm, EDSS 5±2) or to Pilates Group (8 participants, age 70±11 years; weight 69±15 kg and height 169±9 cm, EDSS 3±1). Both groups performed two sessions of physical activity per week during a period of 5 months. Sit and Reach, Sit to Stand, Saliva Antioxidant, Stabilometry were evaluated three times: after the first (T0) and the third (T1) month of physical activity and at the end (T2) of the training period.

**Results:** The ANOVA and post hoc tests showed statistically significant variations. MNS group: Sit to Stand test: T0 vs T2, +13%, ES = 0.59; average COP X: T0 vs T1, -97%, ES = 0.94; COP distance: T0 vs T2, -32%, ES = 1.31; Average speed: T0 vs T2, -32%, ES = 1.31; Distance/Surface: T0 vs T1, -55%, ES = 0.86, T0 vs T2, -53%, ES = 0.83. Pilates group: Sit and Reach test: T0 vs T2, +12%, ES = 0.26; Standard Deviation X: T0 vs T2, -50%, ES = 0.66; COP distance: T0 vs T2, -70%, ES = 0.84; Average speed: T0 vs T2, -44%, ES = 2.09; Body Barycentre Ellipse surface: T0 vs T2, -45%, ES = 0.51.

**Conclusions:** Both Multiple Neuromuscular Stimulation and Pilates® exercises were well-tolerated. MNS and Pilates® improve muscle performance, flexibility and body control. Therefore, it is possible to suppose that these combined protocols could be useful to maintain physical capacity and increase the quality of life of patients with MS.

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### EP1835

#### Efficacy of daclizumab beta vs intramuscular interferon beta-1a on patient-reported outcomes across patient demographic and disease activity subgroups in DECIDE

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**Background:** In DECIDE, patients with relapsing MS (RMS) treated with daclizumab beta (DAC BETA) 150mg every 4 weeks reported significantly greater mean improvements from baseline (BL) to Week 96 on the Multiple Sclerosis Impact Scale physical subscale (MSIS-29 PHYS;  $P < 0.001$ ), the EQ-5D visual analogue scale (VAS;  $P < 0.001$ ), and the EQ-5D health utility index (HUI;  $P = 0.005$ ) vs intramuscular (IM) interferon (IFN) beta-1a 30mcg once weekly.

**Objective:** Examine post hoc the effects of DAC BETA vs IM IFN beta-1a on patient-reported outcomes (PROs) in subgroups based on BL characteristics in DECIDE.

**Methods:** The MSIS-29 PHYS and the EQ-5D (VAS and HUI) were assessed at BL and then every 24 weeks. Subgroups included: sex (male, female); age ( $\leq 35$ y,  $> 35$ y); time since diagnosis ( $< 3$ y,  $\geq 3$  to  $< 10$ y,  $\geq 10$ y); relapses in prior year ( $\leq 1$ ,  $\geq 2$ ); EDSS ( $< 3.5$ ,  $\geq 3.5$ ); Gd<sup>+</sup> lesions (absent, present); T2 lesion volume ( $< \text{median}$ ,  $\geq \text{median}$ ); prior disease-modifying therapy (DMT) (yes, no); disease activity (less active, highly active [ $\geq 2$  relapses in year prior to randomization and  $\geq 1$  Gd<sup>+</sup> lesion at baseline MRI]). Analyses were based on ANCOVA, adjusted for relevant BL covariates.

**Results:** Across all subgroups, the DAC BETA group demonstrated greater mean improvement, or less worsening, from BL to Week 96 in MSIS-29 PHYS score vs IM IFN beta-1a; treatment differences were significant ( $P < 0.05$ ) for: female, age  $\leq 35$ y,  $\geq 2$  relapses in prior year, EDSS  $< 3.5$ , Gd<sup>+</sup> lesions present, T2 lesion volume  $\geq \text{median}$ , no prior DMT use, time since diagnosis ( $< 3$ y,  $\geq 10$ y), less and highly active disease activity. At Week 96, vs IM IFN beta-1a, the DAC BETA group also showed greater mean improvement from BL on the EQ-5D VAS (differences significant for: female, male, age  $\leq 35$  y, time since diagnosis ( $< 3$ y),  $\geq 2$  relapses in prior year, EDSS  $< 3.5$ , Gd<sup>+</sup> lesions present and absent, T2 lesion volume  $\geq \text{median}$ , no prior DMT use, less and highly active disease activity) and the EQ-5D HUI (differences significant for: female, age  $> 35$ y, time since diagnosis ( $< 3$ y),  $\leq 1$  relapses in prior year, EDSS  $< 3.5$ , Gd<sup>+</sup> lesions present, T2 lesion volume  $\geq \text{median}$ , no prior DMT use, less and highly active disease activity).

**Conclusions:** DAC BETA demonstrated improvements on PROs vs IM IFN beta-1a at Week 96 across all key subgroups. These effects were observed across all PROs for patients with lower baseline disability (EDSS  $< 3.5$ ) and less time since diagnosis, providing further evidence of the benefits of early treatment on PROs.

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## EP1836

### Improvement of quality of life and its relationship to neuropsychiatric outcomes in patients with multiple sclerosis starting treatment with Natalizumab: a 3-years follow-up multicentric study

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**Background:** Health-related quality of life (HRQoL) is impaired in multiple sclerosis (MS) but can be improved by disease-modifying therapies such as Natalizumab. However, no long-term follow-up post-marketing study about Natalizumab and HRQoL is available and the predictive factors of HRQoL improvement are unknown.

**Methods:** Forty-eight patients with relapsing-remitting MS were included in a 3-year open-label, single group, multicenter, clinical trial (NCT01392872). HRQoL was measured by the MusiQoL questionnaire, together with physical disability, cognition, fatigue, anxiety and depression scores at baseline, 6 months, 12 months, 18 months and 36 months after starting Natalizumab therapy.

**Results:** Compared to baseline, global HRQoL, as measured with the index of the MusiQoL, was significantly increased 6 months after the beginning of Natalizumab therapy ( $58.8 \pm 16.8$  vs  $68.7 \pm 18.9$ ,

$p < 0.001$ , Cohen's  $d = 0.55$ ) and this improvement was maintained over time for up to 3 years. The improvement of the global HRQoL after 18 months was correlated with an improvement of information processing speed performances ( $r = 0.43$ ,  $p = 0.003$  for SDMT) and with a decrease in depression and fatigue scores (respectively  $r = -0.37$ ,  $p = 0.013$  and  $r = -0.52$ ,  $p < 0.001$ ). The variation of the global HRQoL after 3 years was negatively correlated with the variation of fatigue score ( $r = -0.44$ ,  $p = 0.015$ ). Higher fatigue score at baseline was correlated with improvement in global HRQoL 3 years after ( $r = 0.34$ ,  $p = 0.041$ ). Higher depression score and higher physical disability at baseline were correlated with improvement in some dimensions of the MusiQoL and especially in the activities of daily living (respectively  $r = 0.39$ ,  $p = 0.020$  and  $r = 0.39$ ,  $p = 0.018$ ).

**Conclusions:** Natalizumab improved quickly and sustainably HRQoL in patients with relapsing-remitting MS. In terms of HRQoL, Natalizumab seems to benefit mainly patients with higher physical disability, fatigue and depressive symptoms at baseline.

## Disclosure

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JP has received compensation for serving as advisory board and research support from Novartis, Bayer Schering, Merck Serono, Sanofi Aventis, Teva.

BB serves on scientific advisory boards for or has received honoraria or research support for its institution from Biogen-Idec, Merck-Serono, Novartis, Genzyme, Teva, Roche, Medday and Bayer.

PC received travel expenses and serves on scientific advisory boards for Teva-Pharma, Merck-Serono, Novartis, Biogen, Genzyme, Bayer, and Almirall.

#### EP1837

##### Energy expenditure of normal and fast walking in multiple sclerosis

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**Background:** Patients with multiple sclerosis (MS) often suffer from various impairments in gait leading to decrease in walking distance and velocity. Physical rehabilitation in accordance is aimed to improve gait and promote walking practice. To establish effective walking practice, it is of importance to measure oxygen uptake (VO<sub>2</sub>) during walking at a given speed and calculate energy cost of walking (CoW).

**Objective:** To determine whether the energy expenditure during walking at different speeds (normal and fast) in MS patients is related to neurological disability as assessed by the EDSS.

**Methods:** Energy expenditure was measured during normal and fast walking in ambulatory multiple sclerosis (MS) patients with EDSS ≤ 4.5. Gas exchange values were acquired continuously by open spirometry and indirect calorimetry using a portable metabolic device (COSMED K5, It). Oxygen consumption at rest was calculated by averaging 30-second oxygen uptake (VO<sub>2</sub>) values over a 5-minute period of seated rest. Participants then performed normal speed and fast speed walking trials, each continuously for 6 minutes along an indoor 30m corridor. O<sub>2</sub>cost (ml/Kg\*m) was extracted for each speed gait indicating the amount of energy needed to walk one meter was assessed.

**Results:** 60 consecutive MS patients, 32 females, 28 males, mean±SD age 38.2±13.9 years, disease duration 5.9±8.5 years, EDSS 2.2±1.3, BMI 25.1±4.7 were included in the study. Energy expenditure at normal walking was 0.191±0.052 and increased during fast walking to 0.207±0.06. Analysis of energy expenditure both in normal and fast walking was significantly different between patients with EDSS ≤ 2.5 (N=47) and patients with EDSS range between 3.0 to 4.5 (N=13), p=0.006 and p=0.002, respectively.

**Conclusion:** Gait energetic costs of normal and fast walking increase with metrological disability.

#### Disclosure

All author Declare no conflict of interest

#### EP1838

##### A mapping study to compare the educational offerings for patients in the fields of multiple sclerosis and HIV in Europe and Canada

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**Background:** The MS in the 21<sup>st</sup> Century initiative, formed in 2011 and led by a Steering Group (SG) of international multiple sclerosis (MS) specialists and patient advocates, focusses on developing programmes to improve the education of and communication between healthcare professionals (HCPs) and people with MS (PwMS). In 2016, the SG conducted a mapping exercise to capture the existing educational offerings for PwMS in Europe and Canada (Phase 1). Findings from Phase 1 indicated patient resources varied by topic, format and country.

**Objective:** Phase 2 of the research was designed to compare the number and type of patient resources in the field of MS to similar offerings for patients in the field of HIV, which the SG identified as a comparator chronic disease.

**Method:** The Phase 1 methodology was repeated for Phase 2 in Europe and Canada. Desktop research was undertaken using Google search engine. Search terms were based on a pre-determined parameter list from Phase 1 and modified for HIV. Research was conducted across multiple stakeholders including patient associations, pharmaceutical companies and public healthcare/government services. Resources were categorised by topic and format including, websites, information sheets and social media. This research model will be later extended to additional geographies.

**Results:** A total of 454 stakeholders were mapped in 21 countries resulting in the identification of 8,097 resources for HIV; compared to 1,867 resources identified in Phase 1 for MS. Resource formats identified were similar for both diseases: websites were the most common resource format for HIV and MS but represented a higher proportion of overall resources for HIV (74.3%) compared with MS (46.8%). Fewer printed materials were found for HIV (7.8%) than for MS (19.5%). The most frequently identified topics for both HIV and MS included general disease information (treatment information, general guides and lifestyle advice), accounting for 61.8% and 60.1% of resources. There were more resources that dealt with effective patient-HCP communication for HIV (3.1%) compared to MS (0.3%). The origin of the patient information was similar for both: the majority of resources were provided by patient associations/advocacy groups (HIV 69.1% and MS 63.2%).

**Conclusion:** This research demonstrated that there is a large offering of patient educational resources for HIV in Europe and Canada and when compared with the field of MS, suggests PwMS may be underserved.

## Disclosure

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## EP1839

### Relationship between social support and perception of cognitive difficulties in people with multiple sclerosis

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**Background:** Social Support represents formal and informal relationships, with MS patients obtaining emotional, affective and instrumental support. Emotional support reflects the emotional feeling of being loved, the security of trusting someone and having personal intimacy; Affective support is considered as the expression of real demonstrations of love, affection or empathy and Instrumental support refers to access to material resources, such as financial assistance, food and clothing. It has already been documented that social support impacts on the perception of quality of life, but the influence on the perception of cognitive difficulties has not yet been studied.

**Objectives:** To analyze the difference of social support perception between MS patients and Healthy controls (HCs) and to evaluate the association between social support and the MSNQ patient report.

**Methods:** The sample included 105 MS patients (89.2%RR, 8.8%SP and 2.0%PP) and 78 HCs. MS Patients: 74% were female; mean age: 38.88 ± 12.74 years; education: 13.24 ± 3.28 years; EDSS: 2.75 ± 2.11; disease evolution 10.08 ± 9.16 years; depression: 11.91 ± 9.08 (range 0-34) HCs: mean age; 41.50 ± 10.53; education: 14.77 ± 2.10. Outcomes measures: Medical Outcomes Study Social Support Survey (MOS) with 3 dimensions: emotional, affective and instrumental support; Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), Beck Depression Inventory II; EDSS.

**Results:** Affective subscales support ( $t(158) = -2.48, p = .014$ ) and global index ( $t(158) = -2.025, p = .045$ ) of the MOS Scale showed significant differences between MS and HCs. The MSNQ patient report was significantly correlated with the instrumental dimension of social support ( $r = -0.28$ ).

**Conclusion:** Less instrumental social support negatively affects the perception of cognitive deficits in patients with MS.

## Disclosure

Vanotti Sandra: nothing to declare

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## EP1840

### Longitudinal changes in mental toughness, sleep disturbances, and physical activity in patients with multiple sclerosis (MS)

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**Background:** Multiple sclerosis (MS) is a chronic progressive autoimmune disease. fatigue, depression and cognitive impairments are the most common symptoms of patients with MS. Whereas there is extant research on fatigue, depression, and cognitive impairment of patients with MS during the clinical course, no research focused on the long term changes of psychological functioning, sleep problems, and physical activity on these patients. The aims of the present study were therefore to examine changes in physical activity, sleep disturbances, and mental toughness over a 1.5-year period of time in people with multiple sclerosis after the onset their MS.

**Methods:** A total of 18 patients with diagnosed MS (mean age: M = 33.61 years) took part in this study. They completed a booklet of questionnaires covering socio-demographic data, mental toughness, sleep disturbances, and physical activity, at the onset of disease and 1.5 years later

**Results:** 1.5 years after the onset of MS, patients had lower levels of vigorous physical activity, but not statistically significant change in moderate physical activity. Patients with sleep disturbances at the onset of disease had statistically significant sleep disturbances also 1.5 years later. Medication and EDSS scores did not change over time.

**Conclusions:** Compared to the onset of disease, 1.5 years later, patients with MS reported similar mental toughness traits, sleep disturbances and levels of moderate physical activity. The pattern of results of the present pilot study suggests that the onset of MS is not an obstacle for doing moderate physical activity. Based on the result of this study, sleep disturbances remains stable by time.



## Disclosure

All authors declare no conflicts of interest. The entire study was performed without external funding.

## EP1841

### A three month interim analysis of quality of life in patients with relapsing remitting multiple sclerosis in the UK: the Patient Reported Outcomes with Fingolimod in Local Experience (PROFILE) study

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**Introduction:** Data are limited on the quality of life (QoL) of patients with relapsing remitting multiple sclerosis (RRMS) treated with fingolimod, a disease modifying therapy (DMT), in the UK.

**Methods:** Prospective observational study of 144 consenting patients with RRMS in 14 secondary care NHS centres. Eligibility: aged 18-55 years at first initiation of fingolimod ('baseline') and treated within the European product licence. Baseline data collected from medical records: demographics, disease characteristics and DMT history; baseline, 3, 6 and 12 month (M) patient-reported data collected included the EQ-5D-5L, the Multiple Sclerosis Impact Scale (MSIS-29) and adverse events (AEs). Percentages have been rounded so may not total 100%; 95% confidence intervals [CI] presented where available.

**Results:** The results of an interim analysis of n=110/144 patients (76%) who had ≥1 post-baseline assessment of MSIS-29 are presented. Mean (standard deviation [SD]) patient age at baseline: 40 (8) years; n=87 (79%) female; n=5/110 patients (5%) had received no previous MS DMT, 65 (59%) had received 1, 30 (27%) had received 2, and 10 (9%) had received >2. Baseline mean (SD) MSIS-29 physical domain score: 34.7 (23.3); at 3M: 31.4 (22.2); mean change: -3.3 [CI:-5.7,-0.9]. Baseline mean (SD) MSIS-29 psychological domain score: 39.5 (23.8); at 3M: 35.4 (22.7); mean change: -4.2 [CI:-7.8,-0.5]. Baseline mean (SD) EQ-5D utility index score: 0.73 (0.21); at 3M: 0.74 (0.23); mean change: 0.01 [CI:-0.02,0.04]. Baseline mean (SD) EQ-5D visual analogue scale score: 67.9 (18.4); at 3M: 69.0 (17.3); mean change: 1.0 [CI:-2.2,4.3]. The largest increases in patients reporting no problems were in the EQ-5D usual activities subscale: n=38/110 (35%) at 3M, compared to n=27/110 (25%) at baseline, and in the self-care subscale: n=74/110 (67%) at 3M, compared to n=67/110 (61%) at baseline. AEs reported by n=38/110 patients (35%) at 3M; most frequently reported AE: headache (n=7/110, [6%]).

**Conclusions:** Patients reported improved scores in both the physical and psychological domains of the disease-specific MSIS-29 at 3M, indicating an improvement in MS-related QoL following initiation of fingolimod. Overall utility did not change significantly when measured by the EQ-5D, suggesting this generic tool may not be sensitive enough to capture disease-specific factors impacting on QoL. Forthcoming study assessments at 6 and 12 months will support understanding of longer term QoL in this patient group.

## Disclosure

Nick Adlard was an employee of Novartis Pharmaceuticals Ltd, the sponsor of the PROFILE study, at the time of the study.

Fiona Brisbane is an employee of Novartis Pharmaceuticals Ltd, the sponsor of the PROFILE study.

Jane Watson is an employee of Novartis Pharmaceuticals Ltd, the sponsor of the PROFILE study.

Michel Kroes is an employee of Novartis Pharmaceuticals Ltd, the sponsor of the PROFILE study.

Catherine Bottomley is an employee of pH Associates, the company contracted by Novartis Pharmaceuticals Ltd to provide scientific interpretation of the PROFILE study results and medical writing support.

## EP1842

### Gait and physiotherapy: effectiveness of a physiotherapy circuit training on the ability to walk and quality of life in a multiple sclerosis' s patients

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**Background:** Gait abnormalities are an early clinical symptom in multiple sclerosis (MS), leading to decreased activity and limitations in function. In addition, MS causes sensorimotor deficits and neurological weakness that impairs mobility in daily living activities. There are several studies showing beneficial qualities of physical therapy on walking function, mobility and quality of life. Nonetheless, the circuit training approach hasn't been studied enough in people with MS and gait and quality of life. Previous studies have shown that physiotherapy circuit training is a good method to improve locomotor function and mobility in stroke survivors.

**Objective:** The aim of this study was to evaluate the effect of a physiotherapy circuit training on gait parameters and quality of life in people with MS.

**Methods:** An experimental trial with a sample of 60 subjects. 41 females and 19 males with relapsing-remitting (n=43), secondary progressive (n=6) and primary progressive (n=11) MS with EDSS of 1.5 to 5.5. They were randomly assigned to 2 groups: experimental group (n=30) received 12 physiotherapy circuit training sessions over 3 months (2 hours/each session), whereas control group were in wait list. The sessions included four different workstations: Balance trainer, whole-body vibration platform, Biofeedback cycling and treadmill with body weight support. Outcome for the gait, registered by Gaitrite Walkway System were: velocity, cadence, step length differential, ambulatory time and Functional Ambulatory Profile (FAP). Quality of life was assessed by: MusiQoL, a specific self-reported questionnaire of health related quality of life. Date registered before and after the intervention.

**Results:** Significant difference in the experimental group in FAP (p< 0.03), ambulation time (p< 0.32) and step length differential (p< 0.034) after the intervention. No changes in gait pattern were reported in the control group. The quality of life improved but it was not significant (p< 0.092).

**Conclusion:** The physiotherapy circuit training seems to be effective to improve gait patterns in MS patients, moreover it might have a positive influence in the quality of life.

## Disclosure

Anabel Granja: nothing to disclose

**EP1843****The impact of nurse advisors and online advice services on treatment adherence in multiple sclerosis (MS)**A. Altenbuchner<sup>1</sup>, S. Haug<sup>1</sup>, C. Mohr<sup>2</sup>, U. Scorna<sup>1</sup>, K. Weber<sup>1</sup><sup>1</sup>Department of Social Research and Technological Impact Assessment (IST), <sup>2</sup>Faculty of Social and Health Science, Ostbayerische Technische Hochschule Regensburg (OTH), Regensburg, Germany

**Background:** The Active-with MS support program (AMSP) supports patients receiving immunomodulatory disease-modifying therapy with Copaxone®. The AMSP involves three face-to-face consultations with MS nurses in the first half year of treatment. The program also includes a telephone consultation service team and an online forum. The aim of this study is to evaluate the AMSP and explore its impact on treatment adherence and discontinuation.

**Methods:** This social science panel study is based on a mix of methods, combining qualitative guideline-based expert interviews (n= 7 patients; n=7 MS nurses; n=7 service team members) and a standardized postal survey of patients in a longitudinal evaluation with three data collection waves ( $n_{W_1}=87$ ,  $n_{W_2}=65$ ,  $n_{W_3}=37$ ). The third wave involved a standardized online survey of MS nurses (n=86). Analysis of data was conducted by a bootstrap resampling method.

**Results:** Patients said they felt to be part of the treatment decision making (M=4.49, SD=.742). They also have high levels of confidence in their treatment (M=4.14, SD=.883) and in the effectiveness of the advice provided by the MS nurses (M=4.46, SD=.774). In the longitudinal study, dosing was omitted on average never to 3.6 times (BCa 95% CI W\_1 [-.02, .53], BCa 95% CI W\_2 [-.33, 2.21] and BCa 95% CI W\_3 [-.04, 3.61]). Dosing regularity increases at Wave 3. The dropout rate of 10.1% is lower than the expected rate of 20-30%.

Both the importance and ratings for MS nurses were higher than for primary care physicians, specialist physicians, the service team and the online forum.

**Conclusion:** Patients responding to the survey have high levels of adherence, which increases as treatment duration progresses. Apart from teaching injection technique, MS nurses play an important role in educating patients, sharing knowledge and providing psychosocial counseling.

**Keywords:** Multiple sclerosis, adherence, MS nurse consultation service, disease coping strategies

**Disclosure**

TEVA commissioned the evaluation of the AMSP and provided research funding to the Institute of Social Research and Technological Impact Assessment (IST) at Ostbayerische Technische Hochschule Regensburg (OTH). The grant was used to employ research assistants and conduct the surveys. The research team has no conflict of interest or financial interests. Distribution of the questionnaires was organized via TEVA to MS nurses. Subjects were invited to participate and received oral information from MS nurses. Participation in the survey was voluntary and anonymous. Neither MS nurses nor subjects received payment for taking part in the study. Data analysis and research findings were independent of TEVA.

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Mrs. Altenbuchner reports personal fees from OTH Regensburg, during the conduct of the study.

Mrs. Scorna reports personal fees from OTH Regensburg, during the conduct of the study.

**EP1844****Fatigue management: occupational therapy intervention in multiple sclerosis for Argentinean population**

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**Objective:** To provide evidence supporting a biopsychosocial conceptual framework for fatigue management based on Occupational Therapy intervention in Argentinean MS patients and its participation impact.

**Design:** This is a study analyzing participation impact before and after implementation of a local fatigue management program.

**Participants:** Fifty-one (N=51) adults with MS who regularly attended a community based, maintenance rehabilitation center.

**Main outcomes:** Modified Fatigue Impact Scale (MFIS), Functional Independence Measure (FIM), The Community Integration Questionnaire (CIQ), visual-analogue scale.

**Results:** Regarding age, all patients reduced Fatigue Severity Scale (FSS), MFIS and improved FIM; those older than 46 also increased CIQ (3,5%). Both genders decreased fatigue, furthermore men increased FIM(1,3%) and CIQ(1,2%). Working patients reduced fatigue scales, those working full time also increased FIM (4,6%). Patients with higher education decreased fatigue and improved FIM (1,3%) and CIQ(2,9%). Regarding years since diagnose, both groups decreased fatigue scores and increased FIM (< 12 years 0,5%; >12 years 4,9%), those with less than 12 years also increased CIQ(2,1%). All types of MS reduced their fatigue; MSRR also improved FIM(0,3%) and CIQ(0,2%); MSPP increased FIM(4,6%). Patients without medication decreased FSS, MFIS and improved FIM(4,5%) and CIQ(2,6%). Patients with selective immunosuppressants decreased FSS and MFIS. Those with classic medication reduced the cognitive subscale of MFIS and improved FIM (2,2%). The average level of quality of life satisfaction after our intervention was of 6,86.

**Conclusion:** Our local Fatigue Management Program applied in Argentinean MS patients has been proven an important and significant tool for OT interventions in all types of MS. Further studies with larger sample sizes are needed.

**Disclosure**

Nothing to disclose

**EP1845****Dynamic contributors to low quality of life in MS along the disease course**

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**Background:** Multiple sclerosis (MS) affects negatively quality of life. The Short Form Health Survey (SF36) measures various aspects of health-related-quality of life (QoL), including physical and mental health. Physical disability and emotional problems seem to have a negative impact on QoL in patients with MS, but their relative importance at different stages could differ.

**Goals:** To identify the main factors influencing QoL in patients with MS and to compare the contributors to low QoL soon after the first MS relapse and later on the disease.

**Methods:** We included 160 MS patients (mean age 43.6±11.2 years, 72.3% women) and 35 healthy controls (HC, age 41.4±10.9 years, 60% women) who completed the SF36. Eight QoL subscales and two composite scores, physical (PCS) and mental (MCS), were calculated. Participants were also evaluated with the Hospital Anxiety and Depression Scale (HADS), Modified Fatigue Impact Scale (MFIS), Pittsburgh Sleep Quality Assessment and Cognitive Reserve. Clinical information including disease duration, Expanded Disability Status Scale (EDSS), 25-foot walk test (25FWT), 6-minutes walk test (6MWT), Paced Auditory Serial Addition test and Symbol Digit Modalities test were recorded in patients.

**Results:** Patients had 11.7±10.5 years of disease duration, median EDSS of 2.0 (range 0-6.5). They presented worse scores in all SF36 metrics compared to HC ( $p < 0.01$ ). EDSS, walk ability measured with 25FWT and 6WT, HADS, fatigue, sleep and cognitive reserve correlated with most subscales of SF36 ( $p < 0.01$ ). In a multivariate model the main predictors of low PCS were worse MFIS, 6MWT and Pittsburgh score (corrected  $r^2=0.52$ ), and the main predictors of low MCS were worse HADS and shorter disease duration (corrected  $r^2=0.41$ ).

Patients with less than 2 years of disease duration ( $n=43$ ), compared to those with more than 15 years ( $n=50$ ), presented better physical QoL, but showed greater loss in QoL in the last year and worse mental QoL scores ( $p < 0.01$ ) despite their HADS values were similar ( $11.9 \pm 7.4$  vs.  $10.7 \pm 7.4$ ,  $p=0.47$ ).

**Conclusion:** Fatigue, walk impairment, low quality of sleep, anxiety and depression symptoms are key elements influencing low QoL in patients with MS, although their relative impact changes along the disease. In early phases, when disability is mild, QoL is already impaired, mainly due to worse perception of their mental health probably related to the recent diagnosis.

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## EP1846

**The 24 hour exercise marathon for multiple sclerosis - to promote benefits of regular physical activity among patients and their supporters**

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**Background:** A positive effect of physical activity in people with multiple sclerosis (MS) has been proven in many studies. Most people with MS do not maintain sufficient level of physical activity, due to a variety of factors (such as a lack of motivation or knowledge, fear, insufficient funds or a lack of support).

**Methods:** We would like to report our experience with an annual event that involves patients, caregivers as well as healthcare professionals. The aim of the event is to motivate patients with MS to remain physically active, to inform family members, sponsors and general public about importance and benefits of physical activity in MS and to raise funds for other physical therapy activities for MS patients organized throughout the year.

**Results:** The origin of this event is in Prague, Czech Republic and was inspired by MS patients who attended regular aerobic-resistance exercise and wanted to share their positive experience with other MS patients. The First 24 hour Exercise Marathon for MS (MARS) took place in 2012 in Prague with 84 participants. This event was very successful and its reputation began spreading and encouraging other patients to get involved. The sixth Exercise Marathon for MS took place on March 3-4, 2017 and involved 3 244 participants, 31 sites across Europe including 7 international sites (France, Switzerland, Poland, Turkey, Slovakia) and 24 sites in the Czech Republic. Each site plans activities relevant to their preferences and possibilities, and always includes physical activity, such as circuit training, yoga, Tai-chi, nordic walking, therapeutic climbing etc. All physical activity is planned and supervised by physiotherapists



specialised/experienced in in MS therapy. Exercise lessons are going on for 24 hours, during which teams consisting of patients, their friends, family members, physicians, nurses, and celebrities and other supporters take turns exercising. Educational activities and presentations take place in a meantime. Reports from participating sites are shared in real time on facebook and other media.

**Conclusion:** We would like to invite all MS centers and other interested groups from anywhere in the world to join the MARS in 2018 !

This event was supported and coordinated by Impuls Endowment Czech Republic.

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## Enhancing CNS plasticity

### EP1847

#### Altered brain connectivity and its changes after physiotherapy in people with multiple sclerosis

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**Background:** Regular physical activity and physiotherapy accelerate the ability of the brain to slow down clinical progression in people with multiple sclerosis (MS). It positively influences impaired clinical functions, fatigue, mental and cognitive functions and the quality of life in the general. But the mechanism of this recovery is still not well described. For a better understanding of the pathophysiological and consequent reparative processes in MS are nowadays widely used imaging methods.

**Aims:** In this study, we want to focus on further in-depth understanding of the mechanism of neuroplasticity in people with MS, in terms of monitoring brain connectivity (centrality, regional homogeneity - REHO) in rest (resting state fMRI) - compared with healthy individuals. Further to describe changes in these reactions after ambulatory facilitation physiotherapy.

**Methods:** 39 patients with MS (mean age 46.7±12.3, Expanded Disability Status Scale - EDSS 4.3±1.7, disease duration 12.1±7.2 years) and 42 healthy volunteers (mean age 43.7±14.8 years) participated in the study. People with MS underwent a two-month program of facilitation physiotherapy

(2x a week, 1 hour). The resting state examination was performed at the beginning and at the end of the therapeutic program.

**Results:** The regional homogeneity (REHO) is more pronounced in the areas of occipital lobe (gyrus fusiform), frontal lobe (superior frontal gyrus) and temporal lobe (inferior temporal gyrus) in patients with MS. On the other side healthy controls have higher REHO in cerebellum and in parietal areas (supramarginal and angular gyrus) and limbic areas (posterior cingulate gyrus). The REHO parameter was not changed after the physiotherapy. The parameter of centrality was positively higher in healthy controls in areas of parietal lobus (superior parietal gyrus), subcortical grey nuclei (nucleus caudatus) and thalamus. After physiotherapy, the centrality was more pronounced in cerebellum, temporal lobe (inferior temporal gyrus) and parietal lobe (supramarginal gyrus).

**Conclusions:** There were found differences in connectivity measures as REHO and centrality between patients with MS and healthy controls. The REHO stayed unchanged after physiotherapy, while the degree of centrality slightly increased.

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### EP1848

#### Dance for health: the preliminary effects of a dance-intervention on cognition and hippocampal activation in patients with MS

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**Introduction:** Previous studies on cognitive rehabilitation in multiple sclerosis (MS) are promising, both for cognitive training as well as exercise. Here, we examined the effect of a dance-intervention on cognition and hippocampal activation in MS patients.

**Methods:** Nineteen MS patients (mean age 44.53 years ± 8.52; 18 females) participated in a structured dance-intervention. Patients were eligible for participation if they met the criteria for mild cognitive impairment (i.e. a score between 1 and 2 SD below norm scores on at least one neuropsychological test or a score of ≥2 SD below norm scores on exactly one test), had no signs of depression and had an expanded disability status scale (EDSS) of ≤6.0. Patients followed two dance-sessions per week (one hour per session) for eight weeks. Before and after the dance-intervention neuropsychological testing (parallel versions) and structural and functional Magnetic Resonance Imaging (MRI) scanning (episodic memory task) at 3T were performed. Subjective cognitive functioning was measured

using the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ). Data were analyzed using Paired Sample T-tests.

**Results:** At follow-up, patients improved on tests for verbal learning and memory ( $\Delta$ score=6.16;  $p < 0.001$ ), information processing speed ( $\Delta$ score=3.74;  $p = 0.017$ ), attention ( $\Delta$ score=5.17;  $p = 0.033$ ) and working memory ( $\Delta$ score=1.47;  $p = 0.039$ ). The MSNQ score decreased with 3.84 points ( $p = 0.035$ ). On MRI, no structural changes were present, while increased activation of the ventral stream (including the hippocampal area) and frontal areas was observed. Decreased activation was seen in the occipital pole and lingual gyrus (all analyses were cluster-corrected,  $Z \geq 2.3$ ,  $p \leq 0.05$ ).

**Conclusion:** Our preliminary results show promising effects of a dance-intervention in MS patients. Improved cognitive functioning was observed, subjective cognitive complaints were reduced and brain/hippocampal activation changed significantly. We do however need to interpret these results with caution, since data collection of patients in the control condition is not yet finished.

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### EP1849

#### Brain atrophy in multiple sclerosis could be ameliorated by aerobic exercise

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**Objective:** Although most disease modifying drugs exert high antiinflammatory effect on multiple sclerosis (MS), their neuroprotective effect is still rather unclear and is subject to many clinical studies. However, even less is known about additional neuroprotective and regenerative strategies in MS. Previous studies on elderly populations and Alzheimer's disease patients suggest a beneficial effect of exercise on neurodegeneration. The aim of present study is to test the effect of aerobic exercise as a strategy to ameliorate functional disability and brain atrophy progression on patients with MS.

**Subjects and methods:** A group of 25 age- and sex-matched patients with MS, treated with fingolimod for  $\geq 6$  months, no

relapses within 3 months prior to start of study and EDSS  $\leq 6.5$ , were randomized into intervention group (IG;  $n=12$ ) and control group (CG;  $n=13$ ). Intervention consisted of 12 weeks of supervised aerobic exercise twice a week (60 minutes' duration).

Baseline 3T magnetic resonance imaging (MRI) was performed at start of study and follow-up at study end. Volumetric analysis of brain structures was performed on baseline MRI and corresponding regional atrophy changes were calculated between baseline and followup MRI scans using automated brain segmentation and deformation analysis techniques (MS Markers; ms.quantim.eu).

Additionally, we measured walking speed with 10-Meter Walk Test, resting state brain-derived neurotrophic factor (BDNF), interleukin-6 (IL6) and interleukin-2 (IL2) serum levels.

**Results:** Exercise improved EDSS score and walking speed in IG, while in CG a slight worsening of both measures was detected, but none of these changes were significant. Statistically significant increase in volume of parahippocampal ( $p=0.001$ ) and precentral gyrus ( $p=0.048$ ), thalamus ( $p=0.039$ ) and frontal lobe ( $p=0.026$ ) was found in IG compared to CG. After 12 weeks, resting state BDNF levels were significantly higher in the IG ( $p=0.004$ ) compared to baseline, while in CG only a mild, but not significant, increase was observed ( $p=0.8$ ). Levels of IL6 and IL2 remained stable in both groups.

**Conclusion:** Our study supports findings from previous studies that certain brain structures remain pliable throughout lifetime and can be modified through simple techniques, like aerobic exercise. Results suggest that regional brain atrophy, reflecting the neurodegenerative process, could be ameliorated by promoting aerobic exercise among patients with MS.

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### EP1850

#### Fingolimod reduces the clinical expression of active demyelinating lesions in MS

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**Background:** New demyelinating lesions may or may not be associated with clinical symptoms depending on the extent of inflammation and individual network plasticity properties. In animal models and relapsing remitting MS, Fingolimod (FTY720) has been proven to reduce neuroinflammation and modulate glutamate-mediated neurotransmission by enhancing

synaptic plasticity and compensating for demyelinating damage.

**Objective:** This study aimed at retrospectively observing whether treatment with FTY720 can attenuate the clinical expression of new lesions.

**Methods:** 103 patients with relapsing-remitting MS switching for inefficacy from first-line injectable therapy with IFN $\beta$ -1a to FTY720 and treated for at least 12 months were included. For each patient, the occurrence of new gadolinium (Gd<sup>+</sup>) enhancing lesions was evaluated during IFN $\beta$ -1a and FTY720 treatment. The number of asymptomatic active lesions was compared for the two treatments.

**Results:** Treatment with FTY720 was associated with a significantly lower number of Gd<sup>+</sup> lesions ( $p=0.01$ ) and higher rate of asymptomatic lesions compared with IFN $\beta$ -1a therapy (88% vs 30.9%,  $p<0.025$ ). Assuming a linear trend between T2 active lesion accrual and annualised relapse rate (ARR), we found that treatment with FTY720 was associated with an increase of 0.04 in the ARR for each new T2 lesion and of 0.06 for each new active lesion against treatment with IFN $\beta$ -1a, which was associated with an increase of 0.29 and 0.33, respectively.

**Conclusion:** FTY720 limits the clinical expression of new Gd<sup>+</sup> enhancing lesions, possibly modulating brain network plasticity in patients with suboptimal response to previous immunomodulating treatments, as well as causing an overall reduction in neuroinflammation.

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The other authors declare that there is no conflict of interest.